FORMULATION AND *IN-VITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF CINNARIZINE

Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai-32

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUICS

SUBMITTED BY

Reg.No. 26103008

Under the guidance of

Dr. V.VENU, M. Pharm., Ph. D.,

DEPARTMENT OF PHARMACEUTICS

J.K.K.NATTRAJA COLLEGE OF PHARMACY

KOMARAPALAYAM - 638 183.

TAMILNADU.

MAY – 2012

Certificates

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *IN-VITRO* EVALUATION OF MOUTH DISSOLVING TABLET OF CINNARIZINE"** submitted by the student bearing **Reg. No. 26103008** to **"The Tamil Nadu Dr. M.G.R. Medical University",** Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled "**FORMULATION AND IN-VITRO EVALUATION OF MOUTH DISSOLVING TABLET OF CINNARIZINE",** submitted to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment to the requirement for the award of Degree of **MASTER OF PHARMACY** in **PHARMACEUTICS**, is a bonafide work carried out by **Mr. V. MOHAN., [Reg. No:26103008],** under the guidance and supervision of **Dr. V. VENU, M. Pharm., Assistant Professor** Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam, during the academic year 2011 – 20012.

Place: Komarapalayam
Date:

Dr. P. PERUMAL, M.Pharm., Ph. D., AIC.,
Professor & Principal,
J.K.K. Nattraja College of Pharmacy.
Komarapalayam-638183,tamil nadu

CERTIFICATE

This is to certify that the dissertation entitled, **"FORMULATION AND *IN VITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF CINNARIZINE",** submitted to The Tamilnadu Dr .M.G.R. Medical University, for the partial fulfillment of Degree of **MASTER OF PHARMACY** in Pharmaceutics, is a bonafied work carried out by **Mr. V. MOHAN, [Reg.No: 26103008],** under my guidance and supervision during the academic year 2011-2012.

This dissertation is now ready for examination.

Dr. R. SAMBATH KUMAR,**M.Pharm.,Ph.D.,**
Professor and Head,
Department of Pharmaceutics,
J.K.K. Nattraja College of Pharmacy.

Dr. V. VENU, M.Pharm., Ph. D.,
Assistant Professor,
Department of Pharmaceutics,
J.K.K.Nattraja College of Pharmacy

DECLARATION

The work presented in this dissertation entitled **"FORMULATION AND *IN-VITRO* EVALUATION OF MOUTH DISSOLVING TABLET OF CINNARIZINE",** was carried out by me, under the direct supervision of **Dr.V.VENU., M.Pharm., Ph.D.,** J.K.K. Nattraja College of Pharmacy, Komarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university and the thesis is ready for evaluation.

PLACE: **Mr. V.MOHAN.,**

DATE: **Reg. No: 26103008.**

Acknowledgement

ACKNOWLEDGEMENT

At the outset, I am thankful to my parents and Friends for blessing me with great strength and courage to complete my dissertation. Behind every success there are lots of efforts, but efforts are fruitful due to helping hands making the passage smoother. So, I am thankful to all those hands and people who made my work grand success.

I am proud to dedicate my humblest regards and deep sense of gratitude and heart felt thanks to late **Thiru. J.K.K. NATTARAJAH CHETTIAR, founder** of our college. I wish to express my sincere thanks to our most respectful correspondent **Tmt. N. SENDAMARAAI** and our beloved Managing Director **Mr. S. OMM SHARRAVANA,** B.Com, LLB., and Executive director **Mr. S. OMM SINGARAVEL,** B.E.,M.S., for enabling us to do the project work.

I take this opportunity with pride and immense pleasure expressing my deep sense of gratitude to our respectable and beloved guide and principal **Dr. P. PERUMAL, M. Pharm., Ph.D., AIC., J.K.K. Nattraja College of Pharmacy,** whose active guidance, innovative ideas, constant inspiration, untiring efforts help, encouragement and continuous supervision has made the presentation of dissertation a grand and glaring success to complete this research work successfully.

I express my heartful thanks to our head of the department**, Dr.V.VENU., M.Pharm.,Ph.D., Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam.** For his indispensable support which enabled us to complete this task vast success.

My glorious acknowledgement to **Dr. K. SENGODAN, M.B.B.S.,** administrative officer for encouraging us in a kind and generous manner to complete this work.

My sincere thanks to **Dr .R. Sambath Kumar,** M.Pharm., Ph.D., Professor and Head of the department **, Mrs. S.Bhama,** M.Pharm., **Mr. K.Jaganathan,** M.Pharm., Lecturer, **Mr. R. Kanagasabai,** B.Pharm., M.Tech., Asst. Professor, Department of Pharmaceutics, for their valuable help during my project

My sincere thanks to **Mr. V.Sekar,** M.Pharm., Ph.D Professor & Head., **Mr. S.Jayaseelan,** M.Pharm., Asst.Professor, **Mr. Boopathy,** M.Pharm., Assistant Professor, **Mr. Senthilraja,** M.Pharm. Asst.Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

I expresses my sincere thanks to **Mr.V.Rajesh,** M.Pharm., P.h.D Professor & Head of the department, **Mrs. M. Sudha,** M.Pharm., Lecturer, **Mr. P. Ashok kumar**, M.Pharm**.,** Ph.D Professor, Department of Pharmacology, for their valuable help during my project.

I express my sincere thanks to **Dr. P. Sivakumar,** M.Pharm., Ph.D**.,** Professor, **Mr. M. Vijayabaskaran,** M.Pharm., Asst. Professor, **Mrs. Vijayanthimala,** M.Pharm, Lecturer, Mrs**. K. Mahalakshmi**, M.Pharm. Lecturer, Department of Pharmacology, for their valuable suggestion and inspiration.

My sincere thanks to **Dr. S.Sureshkumar,** M.Pharm., Ph.D., Professor & Head of the Department of Pharmacognosy and **Mr. M. K. Senthilkumar,** M.Pharm., Asst.Professor, Department of Pharmacognosy for their valuable suggestions.

I express my sincere thanks to **Mr. N. Venkateswara Murthy,** M.Pharm., Asst Professor & Head, **Mr.S.Rajarajan,** M.Pharm., Assisatant Professor. **Ms. S. Thangamani**, M.Pharm., Assistant Professor , Department of Pharmacy practice for their valuable suggestions.

My sincere thanks to **Mr. N. Kadhiravel ,** M.C.A., for his help during the project. I am delighted to **Mrs. V. Gandhimathi,** M.A., M.L.I.S., Librarian., **Mrs. S. Jayakala,** B.A., Asst., for providing necessary facilities from Library at the time of Work. I extend my thanks to **Mr. S. Venkatesan**, Storekeeper,

Mr. **Manikandan**, computer lab Assistant, and **Mrs. Shanthi,** our lab assistant for their help during the project.

I am thankful to all my classmates, friends, and juniors.

It is very difficult task to acknowledge the services to thank all those gentle people. So I would like to thank all those people who have helped me directly or indirectly to complete this project work successfully.

V. MOHAN.,
(Reg. No 26103008).

Dedicated to

Almighty

My Beloved Parents

And My Guide

CONTENT

1. INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage forms [1].

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost[2].

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarded, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as fast water dispersible tablet [3].

The past two decades, there has been enhanced demand for more patient compliant dosage forms. As a result, the demand for the technologies has been

increased 3 fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are being tablets and capsules one important draw back of these dosage forms is the difficulty to swallow.

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliancel.

Dysphagia or difficulty in swallowing is seen to afflict nearly 35% of general population. This disorder is also associated with number of medical conditions including Stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy. Many elderly persons will have difficulties in taking conventional dosage forms (Solutions, Suspensions, Tablets, Capsules) because of hand tremors, and dysphagia [3].

Swallowing problems are also common in young individuals because of their under developed muscular and nervous systems. Other groups who may experience problems in swallowing solid dosage forms, mentally ill, the developmentally disabled, un co-operated patient and reduce liquid intake plans or nausea. In some cases such as motion sickness sudden episodes of allergic attack or coughing and unavailability of water, swallowing tablet may become

difficult and consequently do not take medications as prescribed which results in high incidence of noncompliance and ineffective therapy.

To fulfill these medical needs pharmaceutical technologists have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast water dispersible tablet , tablet that disintegrates and dissolves rapidly in saliva without need of drinking water. The orodispersible tablet usually dissolves in the oral cavity in about 10 seconds to 3 minutes. Faster the drug goes into solution, the quicker absorption and onset of clinical effect. Some of the drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach, in such cases bioavailability of the drug of significantly greater than those observed from conventional tablet dosage form. The development of orodispersible also provides line extension in market place, product identity, promotion in the sales in market place. These tablets are not only indicated for the people who have swallowing difficulties, but also ideal for active people [3,4] .

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term “orodispersible tablet” for tablets that disperse readily and within three minutes before swallowing.

United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue”. The disintegration time for ODTs generally ranges from several seconds to about a minute[5].

1.1. ORODISPERSIBLE DOSAGE FORM

Mechanism of fast orodispersible tablet [1, 4]

Generally, an orodispersible tablet is a solid-dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less.

"A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

Generally, orodispersible tablets are formulated to disperse rapidly in the mouth, enabling medication to be swallowed without water, thereby increasing convenience and compliance across a broad range of indications and patient types, including the young, elderly, and active patients. Following dispersion, the formulations are typically swallowed, and the drug is absorbed in the same way as conventional solid-oral dosage forms.

"However, orodispersible tablets may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites. The potential for such pregastric absorption rests largely in the physicochemical characteristics of the drug molecule. The intrinsic taste of the drug is also a significant consideration for all orodispersible tablet formulations

Challenges in orodispersible tablet [4]

Although orodispersible tablet formulations offer benefits, there are factors to consider. "The challenges of developing orodispersible tablet formulations products are similar to those for conventional solid oral dosage forms in terms of the need to establish compatibility of the active drug substance with the excipients and process. "In addition, the intended oral dispersion of the units means that the specific taste and mouthfeel characteristics of the drug

substance are particularly relevant." Sweeteners and flavors are typically included to achieve a palatable formulation, but additional taste-masking strategies may also be required such as ion-exchange resins and active pharmaceutical ingredient (API) encapsulation.

"Another challenge is that orodispersible tablet are potentially less robust than conventional solid-oral dosage forms, given their formulation to achieve rapid disintegration (eg. increased friability and greater moisture sensitivity), so packaging requirements need to be considered early in the development process.

As for any other dose form, the bioavailability of orodispersible tablet is governed by the physicochemical characteristics of the API and formulation optimization. "The extent of pregastric formulation is largely dependent on the physicochemical characteristics of the drug, but the formulation may aim to maximize the potential to optimize bioavailability, or minimize the effect to ensure bioequivalence with a per orally absorbed dosage form". Typical formulation variables considered are solubility and particle size of the API, formulation pH, and formulation constituents, in particular taste- masking agents.

Widening the scope of Orodispersible tablet [4]

Industry observers point to broadening uses of orodispersible tablet technology. These include the incorporation of macromolecules using orodispersible tablet into vaccines. "The success for other peptide and protein products will depend on bioavailability requirements and the application of methods to overcome oral absorption barriers," Other areas include: the incorporation of encapsulated APIs to achieve modified-release profiles within the convenience of orodispersible tablet; and the further development of super disintegrants for incorporation into conventional, compressed tablets, potentially widening the opportunity for orodispersible tablet development to non specialist companies.

Thin-film strip technology uses a range of water-soluble polymers and is reported to be able to incorporate water-soluble, insoluble, or taste-masked

ingredients. The film is manufactured as a continuous sheet and then cut into individual doses prior to packing. The major limitations to this technology are the relatively low doses that can be accommodated (approximately 30 mg) and its moisture sensitivity requiring specific unit-dose packaging to protect the product and ensure shelf life.

Advantages of the Orodispersible tablets for patients [1,4,5,6]

- Ease of administration to the patient who can not swallow, such as the elderly stroke victims, bed ridden patients, patients affected by renal failure and who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Achieve increased bioavailability / rapid absorption through pre-gastric absorption of drugs from the mouth, pharynx and esophagus as saliva passes down.
- Convenient for administration and patient complaint for disabled, bedridden patients and for travelers and busy people who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking of suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Limitations of Orodispersible Tablet

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.

- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Counseling Points for Orodispersible tablet [1]

Pharmacists are in the ideal position to become familiar with the different technologies, and educate their patients on what to expect upon taking their first dose. The majority of patients receiving Orodispersible tablet preparations have little understanding of this new dosage form. Patients may be surprised when tablets begin to dissolve in the mouth. They might expect a faster onset of therapeutic action. Clarification from the pharmacist can avoid any confusion or misunderstanding. As with all dosage form technologies, some patient populations are better served by their use than others. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with S Jogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. Decreased volume of saliva may slow the rate of dissolution/disintegration and decrease the bioavailability of the product.

Although chewable tablets have been on the market for some time, they are not the same as the new Orodispersible tablet. Patients for whom chewing is difficult or painful can use these new tablets easily. Orodispersible tablet can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.

Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets.

1.2. REQUIREMENTS OF ORODISPERSIBLE TABLET

An Ideal Orodispersible tablet should:

- Require no water for oral administration, yet dissolve / disperse disintegrate in mouth in a matter of seconds,
- Have a pleasing mouth feel,
- Have an acceptable taste masking property,
- Be harder arid less friable,
- Leave minimal or no residue in mouth after administration,
- Exhibit low sensitivity to environmental conditions,
- Allow the manufacture of the tablet using conventional processing and packing equipment.
- Dose lower than 30mg.
- Ability to permeate oral mucosal tissue

DESIRED CRITERIA FOR MOUTH DISSOLVING DRUG DELIVERY SYSTEM [5,6]:

The tablets should

- Not require water to swallow, but is should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable with taste masking.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

SALIENT FEATURES OF MOUTH DISSOLVING TABLET [5,6]:

- Ease of administration to patient who refuses to swallow tablets, such as pediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Rapid dissolution and absorption of drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

1.3. FORMULATION ASPECTS IN DEVELOPING ODT[5]

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as

- Mehanical strength of tablets
- Taste and mouth feel
- Swallowability
- Drug dissolution in saliva
- Bioavailability
- Stability

The major advantages with effervescent formulation approach that it is a well established, easy to implement and mask the bitter taste of drug[9]. The effervescent system is generally composed of dry acid and dry base, which when react facilitate a mild effervescent reaction when the tablet contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of

carbon dioxide, water and salt. Due to evolution of carbon dioxide, the bitter taste of drug is also masked and a pleasant mouth feel is felt.

Direct compression is the easiest method to manufacture mouth dissolving tablets (MDTs). The great advantage of direct compression is its low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps. In many cases the disintegrants used have a major role in the disintegration and dissolution process of fast disintegrating tablets made by direct compression method. The choice of a suitable type and an optimal amount of disintegrant is important for ensuring a high disintegration rate. The addition of other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties[10]

1.4. THE VARIOUS PROCESSES EMPLOYED IN FORMULATING ODTS ARE AS FOLLOWS

Freeze drying or lyophilization

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation.

Molding

Tablets produced by molding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy flos matrix is then milled and blended with active ingredients and exipients and subsequently compressed to ODT.

Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. The composition contains a bulking agent (mannitol and lactose), a disintegrant (sodium starch glycolate and croscarmellose sodium), an acidic ingredient (citric acid) and/ or alkaline ingredients (sodium bicarbonate), which when compressed into tablets show fast disintegration and enhanced dissolution.

Mass extrusion

This technology involves softening the active blend using the solvent, mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product and cutting into even segments upon heated blade to form tablets.

Sublimation

This method includes the addition of a sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent, a sublime salt (camphor/ ammonium bicarbonate), a binder and other excipients are blended and tablets are prepared. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength.

Sugar based excipient

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose and polydextrose have been used as bulking agents. Because of their high aqueous solubility and

sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials.

Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agents. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As a consequence, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance. Disintegrants have major role in the disintegration and dissolution process of mouth dissolving tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.

1.5.DISINTEGRANTS AND MECHANISM OF ACTION

A disintegrant is an excipient, which is added to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. Disintegration mechanisms are complex processes. They depend first on the excipients used, but also on the properties of the active material.

The proposed mechanism of action of disintegrants include:

1. Water uptake through wicking.
2. Swelling
3. Deformation (shape recovery)

4. Particle repulsion
5. Heat of wetting.

Disintegrants usually work in following ways

1. **Wicking** Water transport into the tablet.
2. **Swelling**: Particles absorb water and expand, like a dry sponge, pushing against the interior of a tablet or capsule causing it to fall apart or discharge its contents.
3. **Elastic recovery**: Stored potential energy is released from disintegrant particles after contact with a fluid environment.
4. **Repulsion**: Electrostatic forces separate the particles.

Wicking and Swelling

A superdisintegrant has to transport water into the tablet centre very quickly (capillary) and has to swell itself at the same moment. As soon as the water penetrates the tablet, it disrupts interparticular matrix bonds causing the tablet to fall apart. To accelerate water transportation, very often powdered cellulose or microcrystalline cellulose is used.

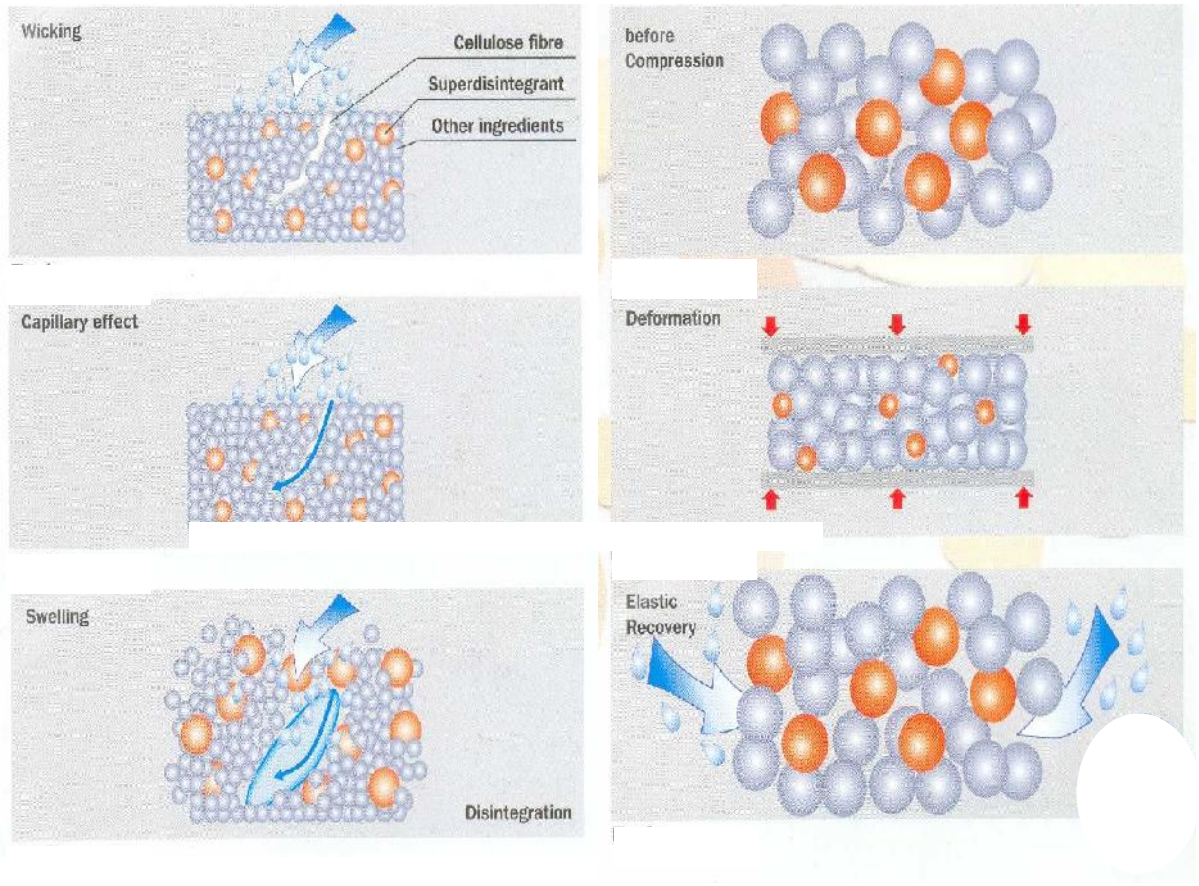
In the disintegrating tablet, the disintegrant volume increases. During this process the space between matrix particles is filled and after very short time, the particles are separated by the force of the swelling disintegrant.

During swelling, the disintegrant undergoes a deformation that means a force, which acts against the compressed particles.

Elastic recovery

Most materials, which undergo a plastic deformation during compression, try to return to their initial shape as soon as possible (stored potential energy). In the tablet matrix, there is no means to recover the former shape. But as soon as water penetrates into the tablet matrix and the forces, which keep the particles together are diminished, those particles have the ability to expand back.

In figure-1: elastic particles are shown before compression (red). After compression, these particles are plastically deformed. After penetration of water into the tablet, these particles return back to their initial shape.



Repulsion:

The principle is that water molecules penetrate a tablet or capsule interior and generate partial positive and negative charges throughout the matrix. This results in the breakdown of particle-particle electrostatic forces of attraction contributing to matrix breakdown.

The later two mechanisms are not well supported by research.

Water penetration is an indispensable pre-processing step for disintegration. The sorption properties of various disintegrants are found to be essential for efficient disintegration and dissolution. If the wetting of the super

disintegrant is slow, for example by coating the disintegrant with a hydrophobic substance, disintegration of the mass is also slowed. The extensive research on super disintegrants has not only implicated the extent of water uptake is important but also have conclusively demonstrated that the rate of water uptake is of critical importance for number of disintegrants.

1.6.PATENTED TECHNOLOGIES

Zydis technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis unit during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Lyoc

Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity.

Quick solv

This technology uses two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

Nano-crystal technology

Nano-crystal technology includes lyophilization of colloidal dispersions of drug substances and water soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drugs.

FlashTab technology

This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, extrusion-spheronization or simple pan coating method. The microcrystals or microgranules of the active ingredients are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

Durasolv technology

The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

OraSolv

The system essentially makes tablets that contain the taste masked active ingredients and an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and releases the active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. The tablets produced are soft and friable.

WOW tab

WOW means without water. This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (lactose, mannitol) and granulated with a high mouldability saccharide (maltose, sorbitol) and compressed into tablets.

Dispersible tablet technology

It offers development of ODT with improved dissolution rate by incorporating 8-10% of organic acids and disintegranting agents. Disintegants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose and cyclodextrins.

Pharma burst technology

It utilizes the co-processed excipients to develop ODT, which dissolves within 30-40s.This technology involves dry blending of dug, flavor, lubricant followed by compession into tablets.

Frosta technology

It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. The process involves usually mixing the porous plastic material with water penetration enhancer and

followed by granulating with binder .The tablets obtained have excellent hardness and rapid disintegration time ranging from 15-30s depending on size of tablets

Oraquick

It utilizes taste masking microspheres technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Oraquick product dissolves within few seconds

Ziplets/Advatab

It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force.

Flash Dose technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consist of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

LITERATURE REVIEW

1.Gohel[29] et al (2004) prepared the mouth dissolved tablets of Nimesulide using vaccum drying technique. Granules containing Nimesulide, camphor, crorospovidone and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The tablets were evaluated for % friability, wetting time and disintegration time. In the present investigation a 3^2 full factorial design was used to investigate combined effect of two formulation variables: amount of camphor and amount of superdisintegrant. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using optimum concentration of camphor and higher percentage of crospovidone.

2Ahmed S. Zidan[30] et al (2006) formulated and optimized mouth dissolving tablets containing Rofecoxib using solid dispersion. The purpose of the present investigation was to increase the solubility and dissolution rate of Rofecoxib by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. For the preparation of Rofecoxib mouth dissolve tablets, its 1: 9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement.

3.Keith J. Simons[31] et al (2006) prepared fast-disintegrating sublingual tablets. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of Epinephrine bitartrate, respectively, and microcrystalline cellulose: low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression, at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the USP limits for weight variation and content

uniformity. At a mean ± SD hardness of ≤ 2.3 ± 0.2 kg, all tablet formulations passed the USP friability test. At a mean ± SD hardness of ≥ 3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively.

4.Abdelbary[32] et al (2004) prepared orally disintegrating tablets using a hydrophilic waxy binder. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. An improvement in tablet hardness and friability was observed with both granulation methods where we were able to obtain RDT with a disintegration time of 40 ± 2 seconds and a hardness of 47.9 ± 2.5N.

5.Koizumi[33] et al (1997) presented an invention, which related to rapidly saliva tablets using sublimation technique. Compressed tablets of Mannitol did not dissolve in water due to the low porosity. To increase the porosity of tablets sublimation was done. Tablets were prepared by direct compression containing mannitol and camphor. A high porosity was achieved due to formation of many pores due to camphor sublimation. The compressed tablets have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

6.Shawn A. Mitchell[34] et al studied a compaction process to enhance dissolution of poorly water soluble drugs using low-viscosity HPMC. The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with low-viscosity HPMC without the use of solvent or heat addition. The compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging method produced comparable dissolution

enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution.

7.Abdelbary[35] et al (2005) determined the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. In the present study, they evaluated the disintegration profile of RDT manufactured by main commercialised technologies, using the texture analyzer. In order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Results obtained when artificial saliva at 37^{o}C was employed as disintegration medium were used to correlate the in vitro and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouth feel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile.

8.Fukami[36] et al (2006) formulated a rapidly disintegration tablet in the oral cavity using a Glycine as a disintegrant. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4kg was 3 seconds. Tablets containing NS-300 showed fastest disintegration compared to other formulations. These results suggest that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behaviors were evaluated. Ethenzamide did not affect the disintegration property; however, ascorbic acid prolonged disintegration time. It was suggested that the tablet formulation containing NS-300 and Glycine was highly applicable to water-insoluble drug, such as Ethenzamide.

9.Shirwaiker[37] et al (2004) prepared fast disintegrating tablets of Atenolol. The preparation contained an active ingredient, sugar (mannitol), superdisintegrant and dicalcium phosphate. Required quantities of each ingredient were weighed, mixed and prepared the tablets by dry granulation. All the formulation had disintegration time of less than 70 seconds. Among the three superdisintegrant Ac-Di-Sol showed the highest efficacy. Formulation containing 10 % Ac-Di-Sol showed the least disintegration time of 30 ± 2 seconds compare to Explotab and Polyplasdone XL.

10.Mishra [38] et al (2005) prepared rapidly disintegrating tablets of Valdecoxib. The poor aqueous solubility of the drug results in variable dissolution rate and poor bioavailability. In the present, invention tablets were prepared using various superdisintegrant following direct compression. All formulation showed disintegration time of less than 60 seconds along with rapid *in vitro* dissolution. All the formulation showed more than 70 % dissolution in 30 min.

11.Amin[39] et al (2005) presented an invention, which relates to fast disintegration tablets for oral administration. Taste masked adsorbents of Ofloxacin were prepared using cationic exchange resins. Taste evaluation of tablets showed complete masking of the bitterness of Ofloxacin. The taste-masked complex of the Ofloxacin was further incorporated into mouth dissolve tablets in combination with Metronidazole benzoate. All the formulation exhibited an in vitro dispersion time less than 50 seconds.

12.Remon[40] et al (1997) prepared the rapidly disintegrating tablets by lyophillization. Tablets contained hydrochlorothiazide, Maltrodextrin, hydroxyethylcellulose and gelatin. The solutions were poured into blisters and freeze dried. Maltrodextrin could be a filler of choice for the production of

lyophilized tablets as freeze-drying due to amorphous network, which dissolved in the water with seconds. They evaluated gelatin, xanthan gum and hydroxyethylcellulose a binding agents in the formulation of freeze dried tablets with Maltrodextrin as filling agents.

3.1. AIM AND OBJECTIVE

Aim of the present work is to formulate Cinnarizine Orodispersible tablet by using solid dispersion technique and different superdisintegrants and evaluating its characteristics.

Now a day fast dissolving tablets are gaining more importance in the market. Clinically, histamine H_1-receptor antagonists are the most frequently prescribed drugs in treatment of motion sickness, vomiting, allergic reaction, vertigo and insomnia

.

Conventional Cinnarizine tablets available in market are not suitable where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric and pediatric patients who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and do not have an easy access of water.

To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrants (polymers) and dissolves/disperses in saliva and can be administered without need of water.

Cinnarizine is practically insoluble in water and its dissolution rate is limited by its physicochemical properties .For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets. Because, faster disintegration tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug.

Though, fast disintegrating tablets are prepared by many processes direct compression using superdisintegrants is more preferred method since it is economical and includes less procedure steps.

3.2. OBJECTIVE

- To study the effect of solid dispersion technique on dissolution rate, disintegration time and wetting time was studied.
- To study the effect of various superdisintegrants on disintegration of mouth dissolving tablets.
- To improve the patient compliance by formulating mouth dissolving tablet.

.

.

4. PLAN OF THE WORK

.

- Selection of drug.
- Preformulation studies.
    - Bulk density
    - Tapped density
    - Angle of repose
    - Carr's index
    - Hausner's ratio
- FT-IR study
- Construction of Calibration curve
- Preparation of Solid dispersion by solvent evaporation method.
- Selection of method for Mouth Dissolving Tablets.
- Formulation of Mouth Dissolving Tablets with different superdisintegrants.
- Evaluation of Mouth Dissolving Tablets
    - Thickness
    - Hardness
    - Weight variation
    - Drug content uniformity
    - Disintegration time
    - Wetting time
    - Water absorption ratio
    - In-vitro dissolution study

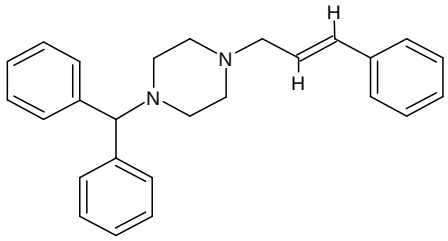
- Stability studies of Mouth Dissolving Tablets as per ICH guidelines.

5.DRUG AND EXCIPIENT PROFILE

I. CINNARIZINE (DRUG) [62,63,64,65,66]

1. Generic Name : Cinnarizine

2. Stucture:



3.CHEMISTRY

IUPAC Name : (E)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl) piperazine

Empirical Formula : $C_{26}H_{28}N_2$

Molecular Weight : 368.514 g/mol

Melting Point : 118°C to 122°C

Solubility : Powder, practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in alcohol and in methanol.

Water Solubility : 750 mg/L

4.PHYSICAL PROPERTIES[63]

Description : A white or almost white and tasteless powder

Storage : Store in a well-closed container, protected from light.

5.PHARMACOLOGY

Category[64, 65] : Anti-Allergic Agents

Histamine H_1-receptor antagonist

Calcium Channel Blockers

Mechanism of action

Binds to the Histamine H_1 receptor and to muscarinic acetylcholine receptors. Cinnarizine also inhibits contractions of vascular smooth muscle cells by blocking L type calcium channels. Cinnarizine has also been implicated in binding to dopamine D_2 receptors.

Pharmacological actions

Cinnarizine is an antihistamine and a calcium channel blocker. Histamines mediate a number of activities such as contraction of smooth muscle of the airways and gastrointestinal tract, vasodilatation, cardiac stimulation, secretion of gastric acid, promotion of interleukin release and chemotaxis of eosinophils and mast cells. Competitive antagonists at histamine H_1 receptors may be divided into first (sedating) and second (non-sedating) generation agents. Some, such as Cinnarizine also block muscarinic acetylcholine receptors and are used as anti-emetic agents. Cinnarizine through its calcium channel blocking ability also inhibits stimulation of the vestibular system.

Pharmacokinetics

Cinnarizine is absorbed from the gastro-intestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral administration. It undergoes metabolism and half life of 3 to 6 hours. Cinnarizine is excreted in the faeces mainly as unchanged drug, and in the urine predominantly as metabolites.

After a single 75 mg dose of cinnarizine, peak plasma level of 160 ± 130 ng/ml occurred after mean time of 3.0 ± 0.45 hours. Plasma concentrations declined with a half life of 3.04 hours. The mean AUC was 925µg/ml/hr. Less than 20% of isotopically active Cinnarizine appears in the urine and about 40% in the faeces.

Half life **:** 3 -6 hrs

Dose **:** 25 mg to 75 mg (three times in a day)

Indication **:** Vertigo, Vomiting

Nausea, Motion sickness

Vestibular symptoms

Adverse effects **:** Sedation, Dizziness

Headache, Hypersensitivity

Dry mouth.

II.POLY VINYL PYROLIDINE

Synonym:

Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Functional category:

Disintegrant; dissolution aid; suspending agent; tablet binder.

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Melting point:

Softens at 150°C.

Stability and storage condition:

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C;

Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

Safety:

When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone. Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.

Application:

In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents.

Also used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

III.AGAR

Description:

Agar is a dried, hydrophilic, colloidal polysaccharide complex extracted from the agarocytes of algae of the Rhodophyceae. The structure is believed to be a complex range of polysaccharide chains having alternating a-(1!3) and b-(1!4) linkages. There are three extremes of structure noted: namely neutral agarose; pyruvated agarose having little sulfation; and a sulfated galactan. Agar can be separated into a natural gelling fraction, agarose, and a sulfated nongelling fraction, agaropectin.

Physical Characteristics:

Agar occurs as transparent, odorless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow colored, or colorless. Agar is tough when damp, brittle when dry.

Functional Category

Emulsifying agent; stabilizing agent; suppository base; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications:

Agar is widely used in food applications as a stabilizing agent. In pharmaceutical applications, agar is used in a handful of oral tablet and topical formulations. It has also been investigated in a number of experimental pharmaceutical applications including as a sustained-release agent in gels, beads, microspheres, and tablets.

It has also been reported to work as a disintegrant in tablets. Agar has been used in a floating controlled-release tablet; the buoyancy in part being attributed to air entrapped in the agar gel network. It can be used as a viscosity-increasing agent in aqueous systems. Agar can also be used as a base for nonmelting, and nondisintegrating suppositories.

Agar has an application as a suspending agent in pharmaceutical suspensions.

IV.GUM KARAYA

Gum karaya is an exudates of gum obtained from the trees of Sterculla Urens.

Description:

White .papery bark. Crude gum karaya is in the form of tears of variable size or in broken irregular pieces. The colour varies from pale yellow to pinkish brown translucent.

Application and uses:

The major uses of gum karaya is a bulk laxative in view of its ability to form a mucilaginous gel on contact with water. Low grade gum served as a more efficient binder in the briquette. Acceleration of settling rates of first carbonation juice in beet sugar manufacture can be accelerated by the addition of small amount of a dilute solution of a natural gum such as gum karaya.

It also serves as ales adhesive water absorber.gum karaya acts as an emulsifying agent and binding agent by absorbing moisture and stored product. Gum karaya acts as a stabilizer on 0.1% to 1% by increasing the viscosity.

V. ISPAGHULA

Synonym: plantago ovata.

Application and Uses:

Isapghula is mainly used as a dietary fiber, which is not absorbed by the small intestine. The purely mechanical action of isapghula mucilage absorbs excess water while stimulating normal bowel elimination. Although its main use has been as a laxative, it is more appropriately termed a true dietary fiber and as such can help reduce the symptoms of both constipation and mild diarrhea. The laxative properties of isapghula are attributed to the fiber absorbing water and subsequently softening the stool. At the same time, this added bulk causes the stool to be better formed, which can reduce symptoms of diarrhea.

Isapghula is produced mainly for its mucilage content, which is highest in *P. ovata*. The term *mucilage* describes a group of clear, colorless, gelling agents derived from plants. The mucilage obtained from isapghula comes from the seed coat. Mucilage is obtained by mechanical milling/grinding of the outer layer of the seed. Mucilage yield amounts to about 25% (by weight) of the total seed yield. Plantago-seed mucilage is often referred to as husk, or psyllium husk. The milled seed mucilage is a white fibrous material that is hydrophilic, meaning that its molecular structure causes it to attract and bind to water. Upon absorbing water, the clear, colorless, mucilaginous gel that forms increases in volume by tenfold or more.

Isapghula mucilage possesses several other desirable properties. As a thickener, it has been used in ice cream and frozen desserts. A 1.5% weight/volume ratio of isapghula mucilage exhibits binding properties that are superior to a 10% weight/volume ratio of starch mucilage. The viscosity of isapghula mucilage dispersions are relatively unaffected between temperatures of 20 and 50 °C (68 and 122 °F), by pH from 2 to 10 and by salt (sodium chloride) concentrations up to 0.15 M. These physical properties, along with its status as a natural dietary fiber, may lead to increased use of isapghula by the food-processing industry. Technical-grade isapghula has been used as a hydrocolloidal agent to improve water retention for newly-seeded grass areas, and to improve transplanting success with woody plants.

It is suggested that the isabgol husk is a suitable carrier for the sustained release of drugs and is also used as a gastroretentive carrier due to its swellable and floatable nature. The mucilage of isabgol is used as a super disintegrant in many formulations.

VI. MICROCRYSTALLINE CELLULOSE (AVICEL 102) [67]

Microcrystalline cellulose is partially depolymerised cellulose prepared from alpha cellulose.

Category: - Pharmaceutical aid (suspending agent, tablet and capsule adjuvant)

Description: - White or almost white powder, odorless.

Solubility: - Insoluble in water but swells producing a white opaque dispersion or gel, slightly soluble in dilute sodium hydroxide solution.

Microcrystalline cellulose for direct compression tabletting comes in a number of grades like PH 101 (original product) & PH 102 (more agglomerated, large particle size with better fluidity). When compressed, the MCC particles are deformed plastically due to the presence of slip planes & dislocation. A strong compact is formed due to the extremely large number of clean surfaces brought in contact during plastic deformation & the strength of hydrogen bonds formed.

Here Avicel 102 used as diluent cum disintegrant. The mechanism of Avicel 102 is interlocking .The particle size of Avicel 102 is small. The decrease in particle size increases binding strength and decreases disintegration time so here we used Avicel 102.

MCC is found in the concentration of 10-25% as a filler binder disintegrant MCC can be used as a disintegrant at a level of 5-15%. The MCC is effective as a binder in direct compression. Its binding advantages in granulation decrease with an increase in water addition. MCC is useful as a disintegrant when used in proportion of at least 5-15%. The disintegration time of tablets of cation exchange resin was reduced significantly in the presence of MCC.

VII.MANNITOL [67]

Synonyms:

Manita, manna sugar, mannite, 1, 2, 3, 5, 6-hexanehexol, pearlitol.

Description:

Mannitol is a hexahydric alcohol related to mannose and is isomeric with Sorbitol, Mannitol occurs as a white, odourless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Chemical Name: D-Mannitol.

Functional Category:

Sweetening agent, tablet and capsule diluent, tonicity agent, bulking agent for lyophilized preparation.

Application:

Mannitol is primarily used as a diluent (10-90%) in tablet formulation where it is of particular value since it is not hygroscopic and may thus be used with moisture sensitive active ingredients. Mannitol is commonly used as as excipient in the manufacture of chewable tablet formulation because of its negative heat of solution, Sweetness and mouth feel.

Stability and Storage:

It is stable in dry state and in aqueous solution. The bulk material should be stored in a well-closed container in a cool, dry place.

VIII. ASPARTAME

It occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.It is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

IX. PURIFIED TALC

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Empirical formula and molecular weight:

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications: Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties. Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.

Stability and storage conditions:

Talc is a stable material and may be sterilized by heating at 160^{o}C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

X.MAGNESIUM STEARATE[37]

Synonyms : Magnesium Octadecanoate, stearic acid magnesium salt,

Chemical name : Octadecanoic acid magnesium salt.

Structural formula : $[CH_3(CH_2)_{16}COO]_2Mg$.

Description

It is a fine, white, precipitated or milled, impalatable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and adhere to skin.

Functional categories: Tablet and capsule lubricant.

Solubility

Practically in soluble in ethanol, ether, water; slightly soluble in warm benzene and ethanol.

Stability and storage

It is stable and should be stored in well- closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkali and iron salts. most alkaloidal salts.

Application :

It is widely used in pharmaceutical formulations. It is used as lubricant in capsule andTablet manufacture at concentration between 0.25- 5.0 %. It is also used in barrier cream.

6. MATERIALS AND METHODS

6.1. MATERIALS

Table No 1: Materials used

SR. NO.	MATERIALS	SOURCE
1.	Cinnarizine	GlaxoSmithKline Pharmaceuticals Ltd., Nashik, Maharashtra
2.	Agar	Gifted by Signet Chemical Corp.
3.	Gum karya	Gifted by Signet Chemical Corp.
4.	Plantago ovata	Gifted by Signet Chemical Corp.
5.	PVP K30	Sd Fine Chem Limited, Mumbai
6.	MCC	Gifted by Signet Chemical Corp.
7.	Mannitol	Strides Arco Labs, Bangalore
8.	Magnesium Stearate	Nice Chemicals Laboratory
9.	Purified Talc	Sd Fine Chem Limited, Mumbai
10.	Aspartame	Medrich Pharmaceuticals, Bangalore
11.	Phosphate buffer **pH 6.4**	Nice Chemicals Laboratory

Table No 2: Equipment used

Sl. No.	EQUIPMENT	MODEL/ SOURCE
1.	UV-spectrophotometer	1700 Pharmascope, Shimadzu
2.	Digital Balance	BL-220H, Shimadzu
3.	Digital pH meter	Systronic Electronics, Mumbai
4.	Dissolution apparatus	TDT-06 N, Electrolab, Mumbai
5.	IR spectroscopy	1615 series, Perkin-Elmer
6.	Hot air oven	Tempo Instruments & Equipments, Mumbai
7.	Hardness tester	Monsanto Hardness Tester
8.	Friability test apparatus	Riche Rich Pharma,Mumbai
9.	Tablet punching machine	Clit, Ahmedabad
10.	Stability chamber	Osworld JRIC-11, Mumbai

6.2. METHODOLOGY

6.2.1. Preformulation studies:

A) Identification and characterization of drug:

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product[71].

i) Organoleptic Characteristics

The color, odor, and taste of the drug were characterized and recorded using descriptive terminology; the results was

Description- Crystalline Powder,

Taste	-	Tasteless
Odor	-	Odorless
Colour	-	White

ii . Melting point:

The melting point of the drug substances was determined by using melting point apparatus (PMP-D, Veego). The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer and constant heat was applied with the assembly suspended in the paraffin bath. The drug sample was tested in temperature range 100-250^{0}C and point at which drug melts was noted. The melting point is reported in section

Iii) **Solubility:**

Solubility of the Cinnarizine was determined in different solvents like water, 0.1 N Hcl, phosphate buffer pH 6.4, alcohol, acetone etc.

iv) IR absorption spectrum:

FT-IR spectra of drug samples were recorded using potassium bromide (KBr) pellets at resolution of $4cm^{-1}$ for its authentication and to study principle peaks using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu). Dry sample of drug and potassium bromide was mixed uniformly and filled into the die cavity of sample holder and an IR spectrum was recorded. The identified peaks were compared with the principle peaks of reported IR spectrum; thus the samples were authenticated. The FT-IR spectr of Cinnarizine was observed.

v) UV absorption maxima of Cinnarizine

UV scanning was done in Simadzu double beam UV/VIS spectrophotometer using 10 µg/ml drug solutions in the wave length range of(200-400 nm). Phosphate buffer 6.4 used as a blank.

B) PREPARATION OF CALIBRATION CURVE :

In the present investigation, Cinnarizine was estimated by UV/VIS spectrophotometry in phosphate buffer (P^H 6.4).

- **Preparation of stock solution**

Cinnarizine (100mg) was accurately weighed and transferred into the 100 ml standard volumetric flask. It was dissolved in phosphate buffer (P^H 6.4) and volume was made up to the mark (to get a 1000 µg/ml solution). From this 10 ml was pipette out and then diluted upto 100 ml with phosphate buffer the (P^H 6.4) From that solution again 10 ml pipetted out and diluted upto 100 ml in volumetric flask with phosphate buffer the (P^H 6.4) to get a stock solution of 10µg/ml.

- **Preparation of Standard Curve:**

From the stock solution 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml were transferred to 10 ml standard volumetric flasks and diluted with phosphate buffer the (P^H 6.4) upto the

mark to obtain Cinnarizine concentration of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml respectively. Absorbance of each solution was measured at 253.5 nm.

C) DRUG – EXCIPIENT COMPATIBILITY:

The selected polymers were characterized by FT-IR spectroscopy and the FTIR spectra of the pure drug cinnarizine with used excipients like Agar, Gum karaya, Plantago ovate. Microcrystalline cellulose, PVP K30, Aspartame, Mannitol etc.

The instrument was operated under dry air purge and the scans were collected at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

6.2.2 DETERMINATION OF FLOW PROPERTIES:

Angle of repose[72]

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h / r$$

Where, h and r are the height and radius of the powder cone, respectively.

Bulk Density

An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks

on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder / Bulk volume

Tapped Density [72]

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder / Tapped volume

Carr's Index [Compressibility Index] and Hausner's Ratio[72]

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flowability of powder. Carr's index and Hausner's ratio can be calculated from the bulk and tapped density.

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio = Tapped density / Bulk density

6.2.3 Preparation of Solid Dispersion [60]:

Preparation of solid dispersions of cinnarizine:

Solid dispersions of Cinnarizine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier was added (PVP k30 in ratio of 1:3). The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Physical mixture

Physical mixture (PMs) having the same weight ratio were prepared by thoroughly mixing appropriate amounts of Cinnarizine and pvp k30 in a morter until a homogenous mixture was obtained . the result were sieved through a 60# sieve and denoted as PM.

6.2.4 Characterization of solid dispersions of Cinnarizine with PVP K30:

Drug content:

An accurately weighed quantity of solid dispersion equivalent to 25mg Cinnarizine was taken into 100 ml of volumetric flask. Dissolved in phosphate buffer pH 6.4 and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700, Shimadzu Corporation, Japan) at 253 nm.

Phase solubility studies:

Phase solubility studies were carried out by adding excess of drug (20 mg) in screw-capped vials containing 20ml of aqueous solution of different pvp k30 concentration. Then suspensions were continuously stirred on electromagnetic stirrer at 250 and 37o and 300 rpm for three days (this duration was previously tested to be sufficient to reach equilibrium). The suspensions were filtered through 0.22µm membrane filter. The filtrate were suitably diluted and analyzed, spectrophotometrically, for the dissolved at 253nm.

Dissolution study

In vitro dissolution studies of CINNARIZINE in powder form, SDs, and PMs were performed by using the USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5^{o} C throughout the experiment. Samples of dissolution medium (5ml) were withdrawn for 20 min by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 253 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released was calculated and plotted against time.

6.2.5 Preparation of tablets containing solid dispersions of cinnarizine:

Different Cinnarizine mouth dissolving tablets were prepared according to the proportion given in table. The raw materials were passed through a screen (40 mesh) prior to mixing. powdered 1:3 ratio solid dispersion, containing amount equivalent to 25 mg Cinnarizine, was mixed with the other excipients and compressed on a rotator tablet punching machine equipped with flat-faced 10-mm punches. The tablet weight was adjusted to ~250 mg

Direct compression method[23]:

Fast dissolving tablets of Cinnarizine were prepared by **Direct Compression** method according to the formulae given in the Tables.

All the ingredients were powdered separately and passed through # 60 mesh sieve separately. The solid dispersion and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and the tablets were compressed using 8 mm flat round punches to get tablets of 250 mg weight.

Table no 3:Composition of Cinnarizine tablets prepared by direct compression method

INGREDIENTS(mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9
CINNARAZINE solid dispersion PVP K30(1:3)	100	100	100	100	100	100	100	100	100
AGAR	10	15	20	-	-	-	-	-	-
GUM KARAYA	-	-	-	10	15	20	-	-	-
PLANTAGO OVATA	-	-	-	-	-	-	10	15	20
MCC	50	50	50	50	50	50	50	50	50
ASPARTAME	5	5	5	5	5	5	5	5	5
MAGNESIUM STEARATE	2	2	2	2	2	2	2	2	2
TALC	3	3	3	3	3	3	3	3	3
MANNITOL	80	75	70	80	75	70	80	75	70
TOTAL	250	250	250	250	250	250	250	250	250

The quantity of solid dispersions was taken after calculating the dose based on drug content of Cinnarizine**.**

6.3. EVALUATION OF POST COMPRESSION PARAMETERS OF CINNARIZINE TABLETS

Weight variation:

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness and Friability

Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of CINNARIZINE was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The CINNARIZINE content was determined by measuring the absorbance at 220.2 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Disintegration test

Tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker containing 900 ml of distilled water and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

***In vitro* dispersion time**

Tablet was added to 10 ml of pH 6.4 phosphate buffer solution at 37 ± 0.5^{o} C. Time required for complete dispersion of a tablet was measured.

Wetting time and Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

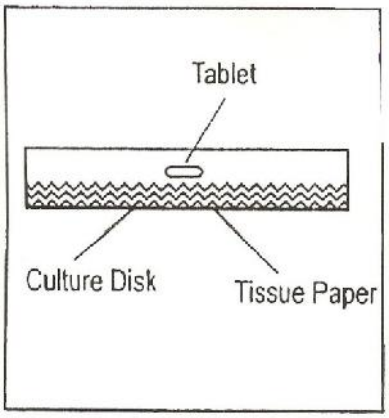


Figure -2: Schematic representation of wetting time /water absorption determination

Water absorption ratio 'R' was determined using following equation

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption

Dissolution study

In vitro dissolution of CINNARIZINE mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5^{o} C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 253 nm The volume withdrawn at each time interval was replaced with fresh quantity of dissolution

medium. Cumulative percent CINNARIZINE released was calculated and plotted against time.

Stability testing

Accelerated stability studies on promising CINNARIZINE formulations D1 and D9 were carried out by storing 15 tablets in amber colored rubber stopped vials at elevated temperature of 40 ± 2^{o} C/75±5% RH (Stability chamber, Osworld) over a period of 90 days (3 months). At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

7. RESULTS AND DISCUSSION

7.1. PREFORMULATION STUDIES:

i) Organoleptic properties

The color, odor, and taste were performed as per procedure .the result were illustrated.

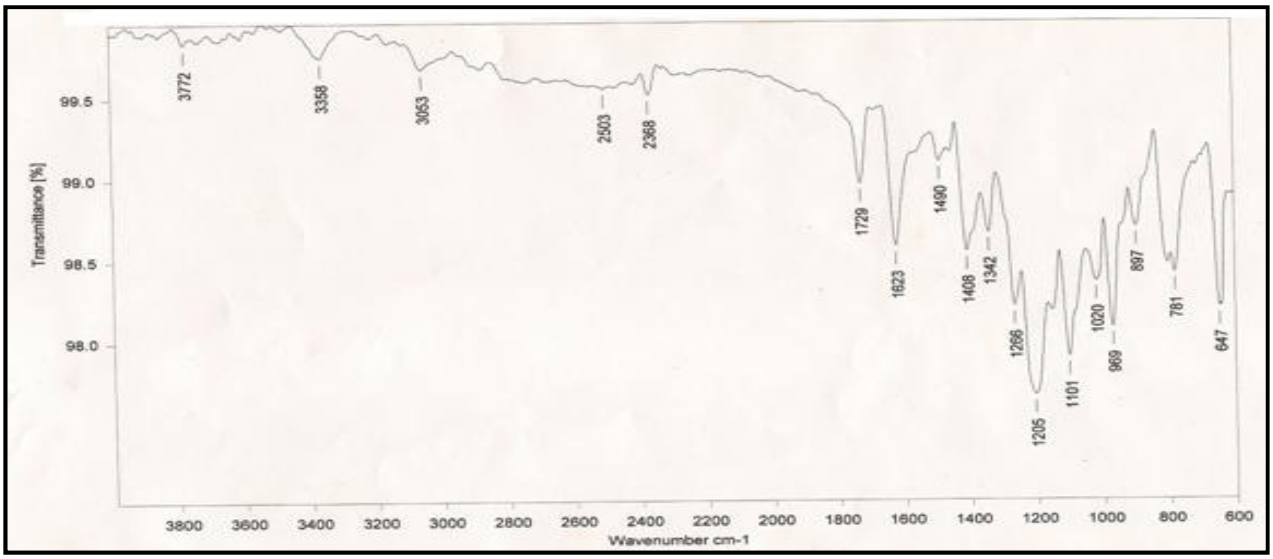
Description	Crystalline Powder,
Taste	Tasteless
Odor	Odorless
Colour	White

ii) Melting point: 118°C to 122° C

iii) Solubility:

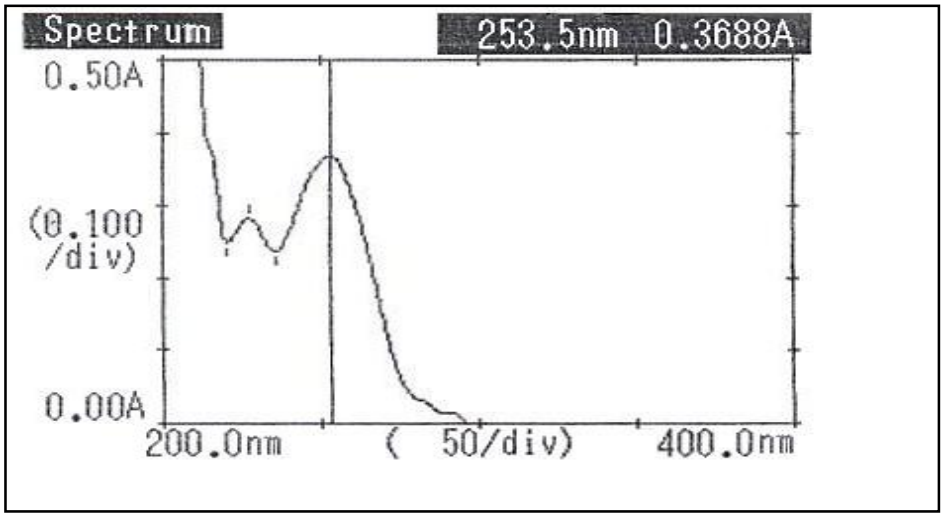
Powder, practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in alcohol and in methanol.

Fig No: 7.1 IR spectrum of cinnarizine tablet



7.2. ESTIMATION OF CINNARIZINE BY UV-METHOD

Figure 7.2: UV absorption spectra of CINNARIZINE in phosphate buffer pH 6.4



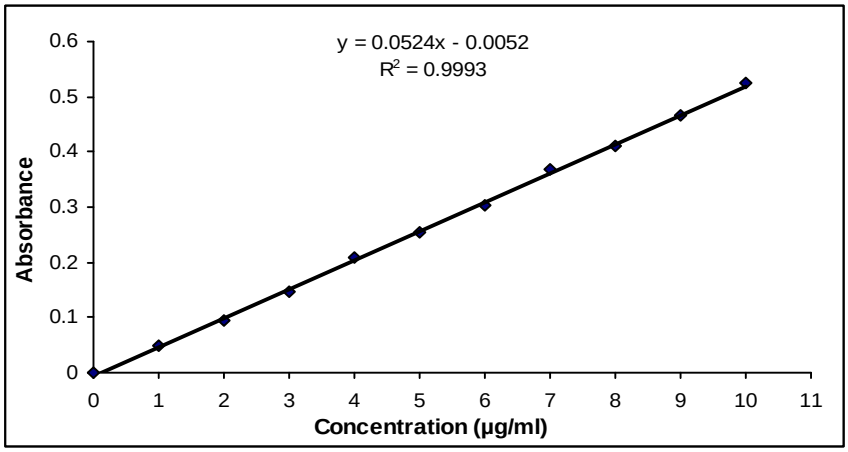
Absorption maximum of cinnarizine was found to be 253.5 nm In phosphate buffer pH 6.4.

7.3 PREPARATION OF CALIBRATION CURVE

Table No 7.1: Standard curve of Cinnarizine in phosphate buffer p^H 6.4.

Concentration (µg/ml)	Absorbance
1	0.049
2	0.096
3	0.147
4	0.209
5	0.253
6	0.304
7	0.368
8	0.411
9	0.465
10	0.524

Fig No: 7.3 Standard curve of Cinnarizine in phosphate buffer p^H 6.4.



7.4 DRUG EXCIPIENT COMPATIBILITY

Fig No: 7.4 IR spectrum of cinnarizine with pvp k30

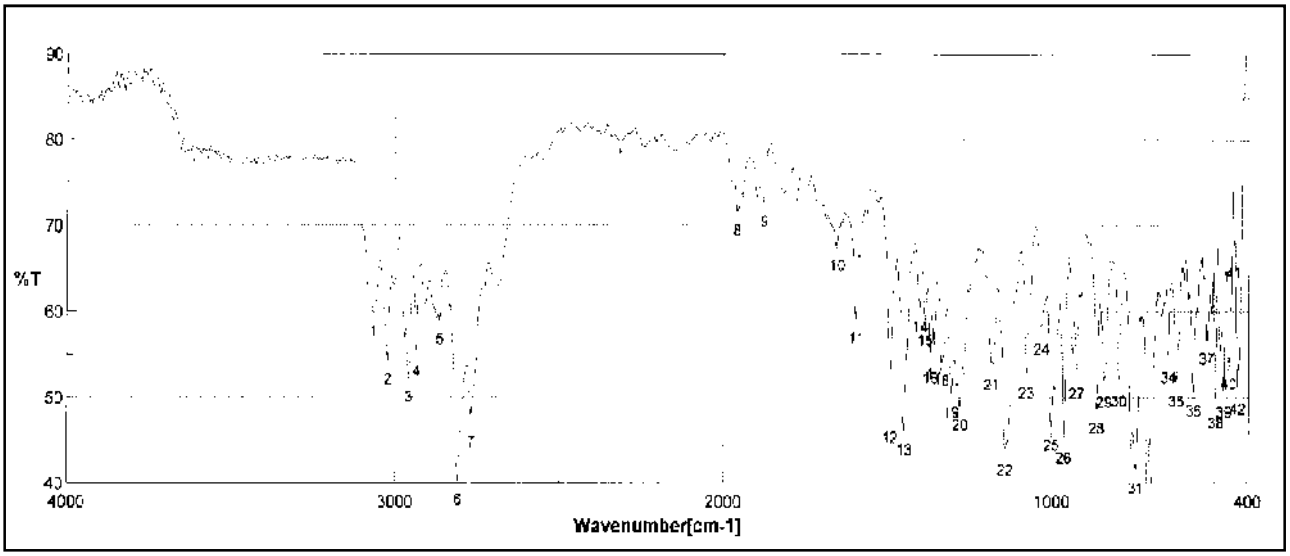


Fig No: 7.5 IR spectrum of cinnarizine with agar

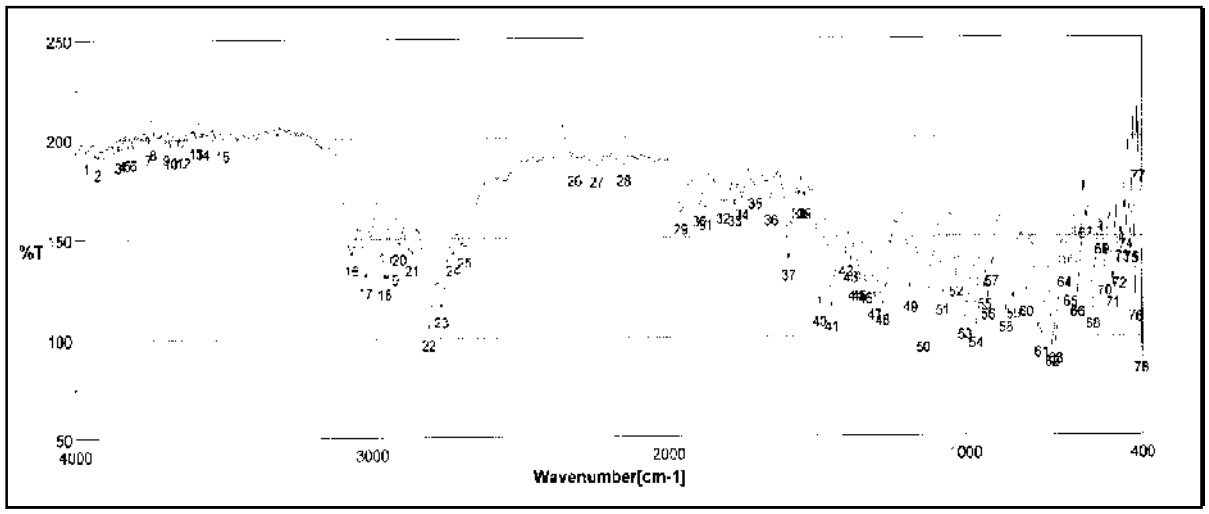


Fig No: 7.6 IR spectrum of cinnarizine with gum karaya

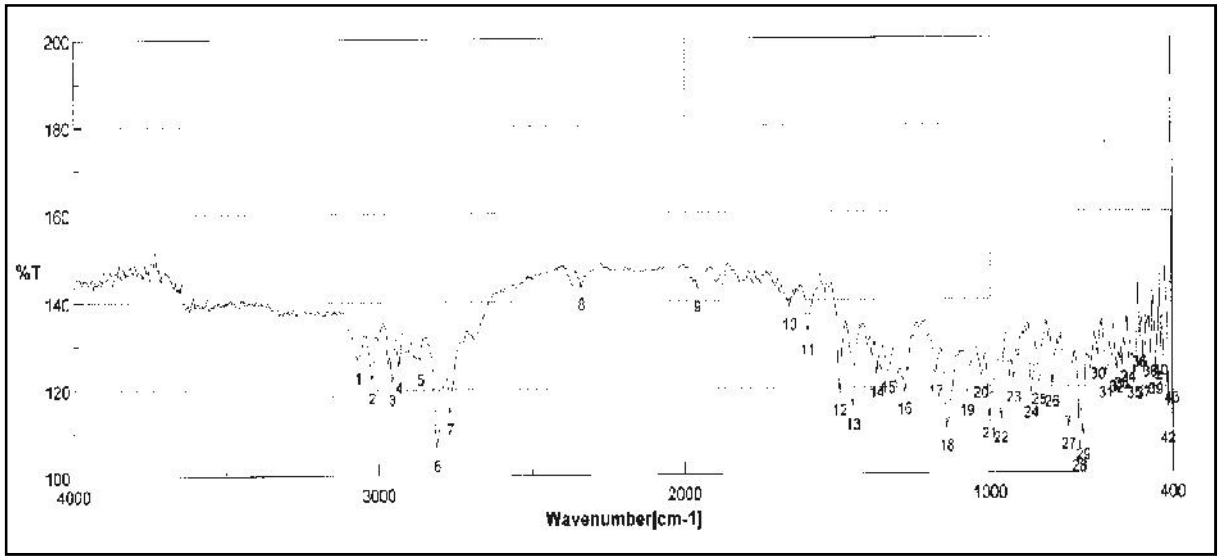


Fig No: 7.7 IR spectrum of cinnarizine with plantago ovata

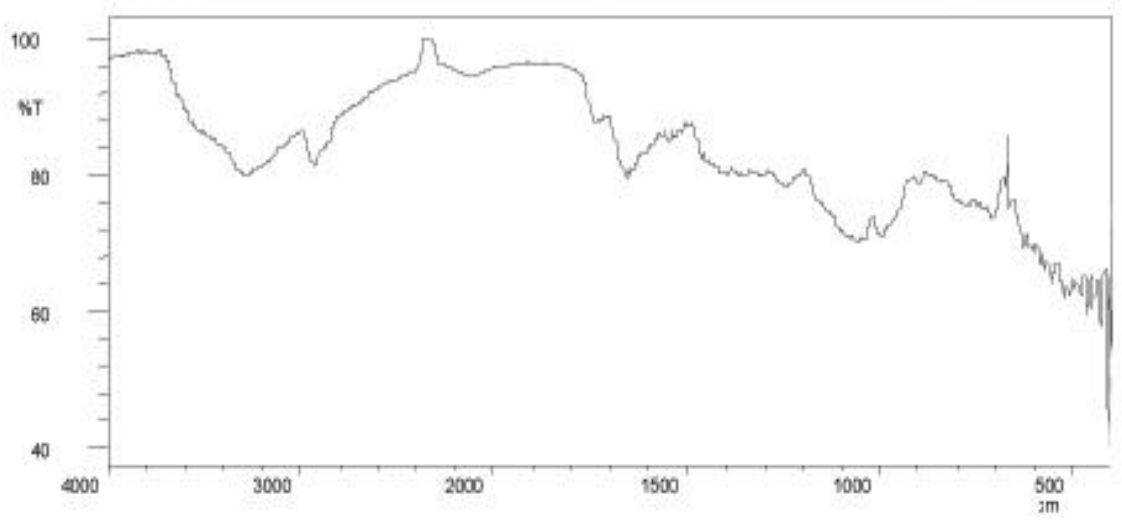
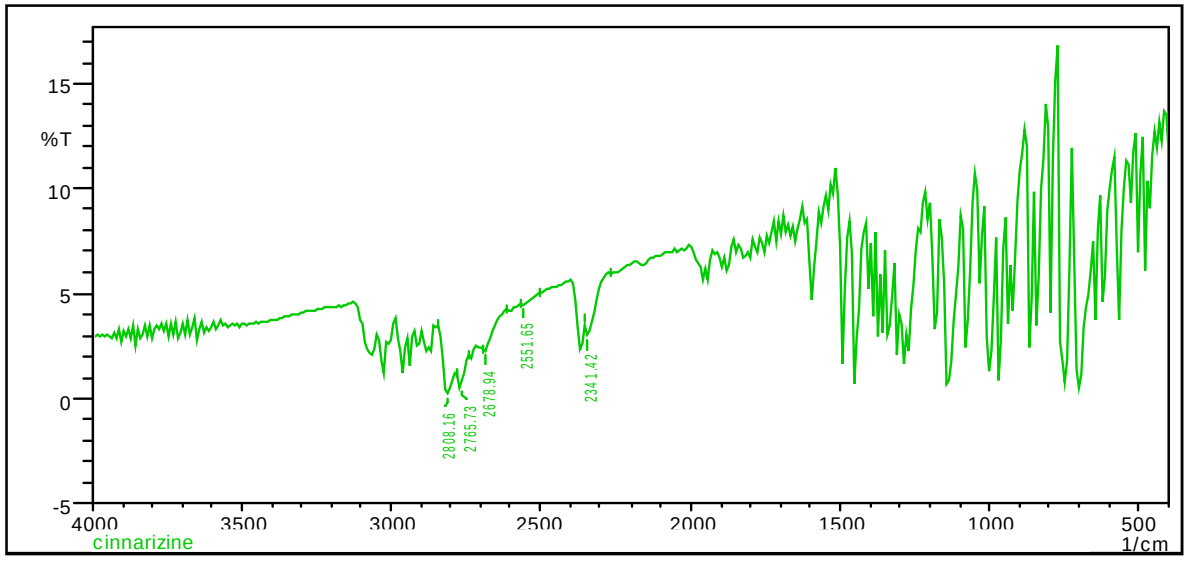


Fig No: 7.8 IR spectrum of cinnarizine with mcc



7.5 DETERMINATION OF FLOW PROPERTIES:

i) Flow properties: (Angle of repose)

Material	Angle of repose
Cinnarizine	27°.85"

ii) Determination of densities

Material	Bulk dencity(gm/ml	Tapped dencity(gm/ml
Cinnarizine	0.28	0.36

7.6 CHARACTERIZATION OF SOLID DISPERSION OF CINNARIZINE

i) Drug content

Table No:7.2 Drug content in physical mixture and solid dispersions.

Solid dispersion (drug to pvp mass ratio)	**Drug content (%)**	**Physical mixture (deug to pvp mass ratio)**	**Drug content (%)**
SD 1:1	96.61	PM 1:1	95.45
SD 1:2	97.98	PM 1:2	96.34
SD 1:3	99.32	PM 1:3	98.42

ii) Dissolution studies of solid dispersions and physical mixtures:

The percentage release of cinnarizine at various time intervals from the physical mixture and solid dispersions made by using various concentrations of PVP K30 . It is evident that dissolution of pure drug is very low, about 30.56% of drug being dissolved

in 20 min. In the 20 min SD containing 1:3 of drug and PVP K30 showed better drug release 99.45% than other ratios of SD's.

Table No:7.3 In vitro dissolution profile of cinnarizine, physical mixture and solid dispersions of cinnarizine in pH 6.4 phosphate buffer.

S . No	Formulation	Cumulative % drug release after 20 min.
1	DRUG	30.56 ± 2.45 %
2	PM 1:1	43.45 ± 2.05 %
3	PM 1:2	47.23 ± 1.67 %
4	PM 1:3	54.73 ± 3.41 %
5	SD 1:1	90.74 ± 1.34 %
6	SD 1:2	96.54 ± 1.40 %
7	SD 1:3	99.45 ± 1.60 %

iii) Comparison Study of Solid dispersion

Table No: 7.4 Comparision of solid dispersions

Time (minits)	Ratio(I:1)	Ratio(I:2)	Ratio(I:3)
0	0	0	0
2	25.73	37.5	52.6
4	39.64	44.24	56.39
6	46.75	52.83	63.12
8	53.14	58.88	68.56
10	61.59	62.61	73.4
12	67.33	68.83	76.81
14	74.97	71.77	80.25
16	80.07	81.64	86.16
18	83.80	90.13	97.55
20	90.74	96.54	99.47

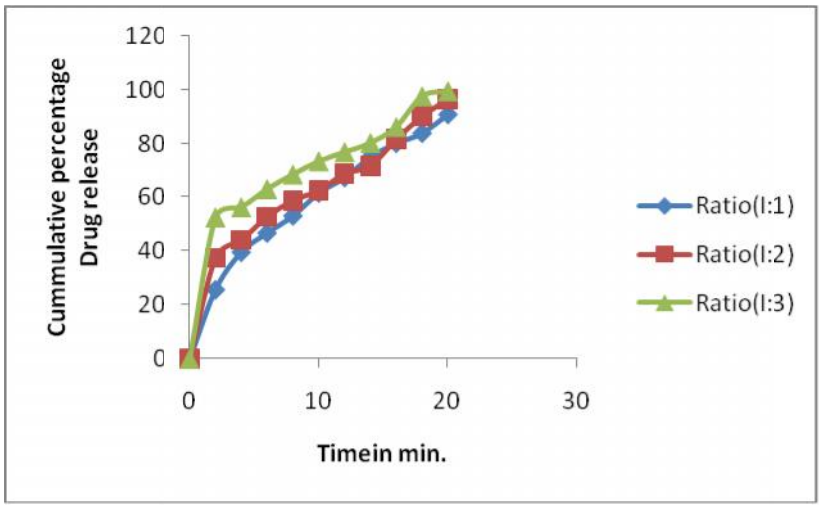
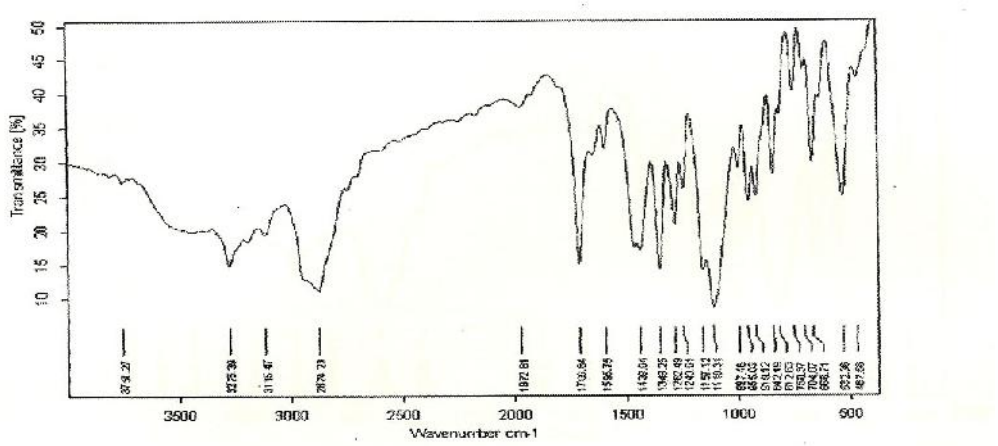


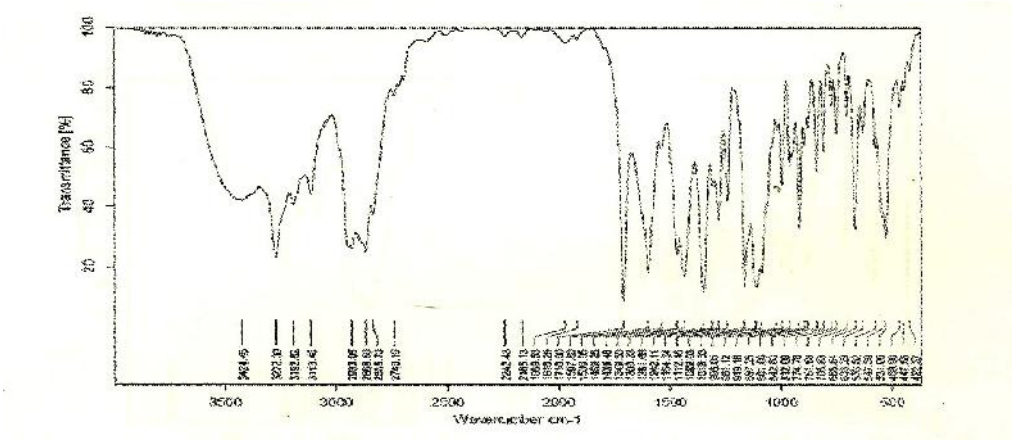
Table No: 7.9 Comparision of solid dispersions

iv) FTIR spectroscopy of Solid Dispersions and Physical Mixtures

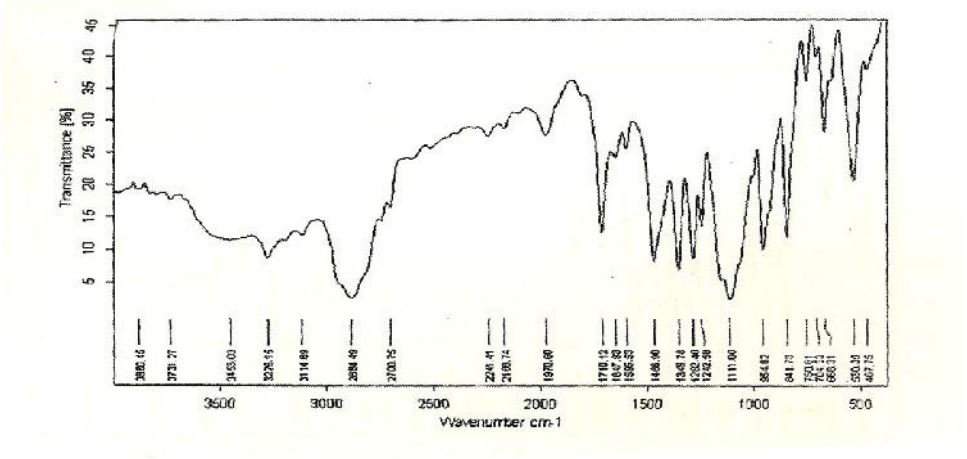
IR spectrum of solid dispersions 1:1



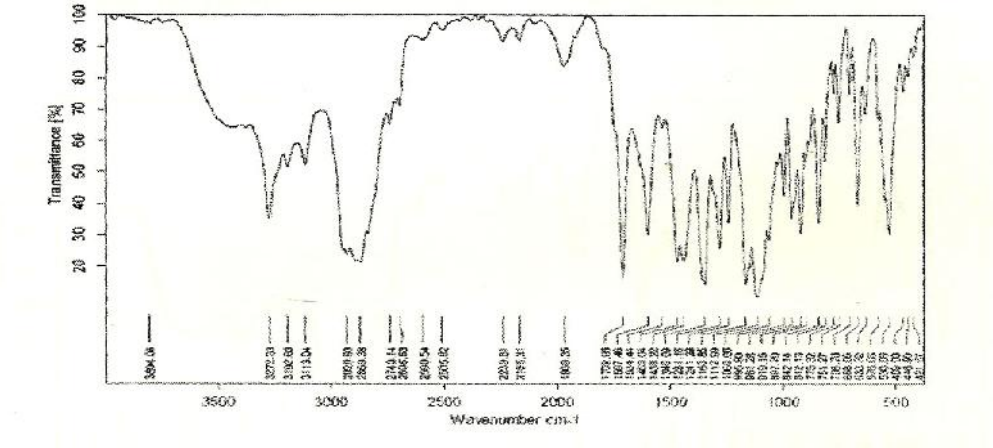
IR spectrum of physical mixture 1:1



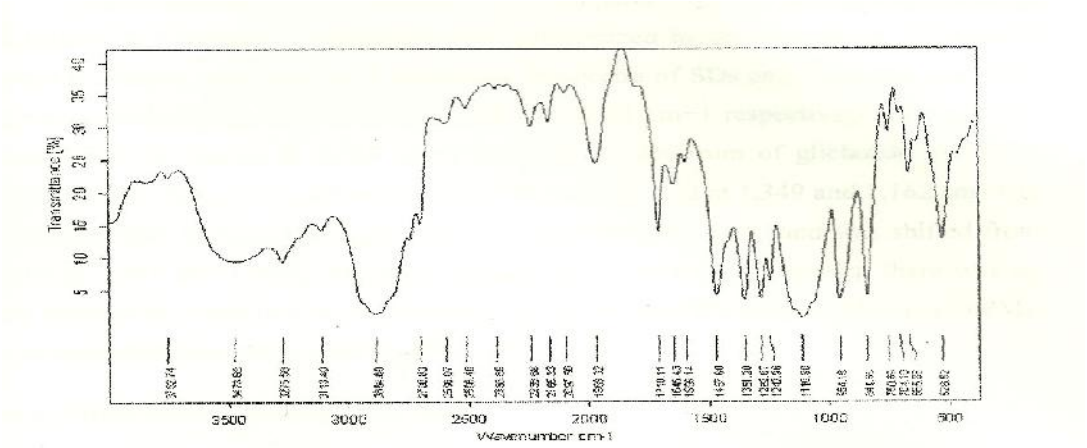
IR spectrum of solid dispersions 1:2



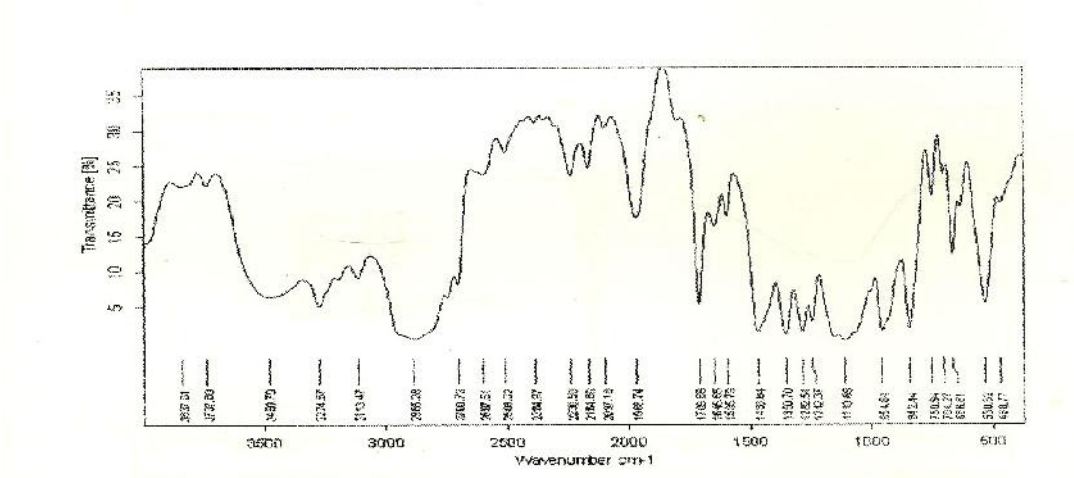
IR spectrum of physical mixtures 1:2



IR spectrum of solid dispersions 1:3



IR Spectrum of Physical Mixtures 1:3



7.6 PRE-COMPRESSION PARAMETERS OF CINNARIZINE TABLETS

Table No 7.4: Pre compression parameters of Cinnarizine tablets

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
D1	0.49	0.57	26.40	14.04	1.16
D2	0.48	0.55	26.06	12.72	1.14
D3	0.46	0.53	23.38	13.20	1.15
D4	0.43	0.49	24.72	12.24	1.14
D5	0.41	0.47	24.94	12.76	1.16
D6	0.39	0.44	25.48	11.36	1.12
D7	0.47	0.64	26.21	14.06	1.16
D8	0.51	0.61	25.74	13.11	1.15
D9	0.46	0.56	23.02	13.79	1.14

*Readings are average of 3 determinations

D1 to D9 indicates formulation containing both solid dispersion and super disintegrants.

7.7. EVALUATION OF CINNARIZINE MOUTH DISSOLVING TABLETS

Table no 7.5: Post compression parameters

S No	Formulation Code	Hardness* (kg/cm^2) ï SD	Friability (%)	*In vitro* dispersion time (s)* ï SD	Percent drug content* ï SD	Weight variation
1	**D1**	3.03 ±0.05	0.32	32.96±1.46	81.35±0.63	247.87±0.56
2	**D2**	2.83±0.05	0.37	33.70±1.45	83.02±2.01	247.70±0.08
3	**D3**	2.83±0.05	0.38	32.88±0.63	80.45±1.11	248.87±0.76
4	**D4**	2.7±0.10	0.33	32.16±0.92	89.94±0.20	248.87±0.39
5	**D5**	2.46±0.05	0.36	30.08±0.75	87.84±0.96	247.17±0.57
6	**D6**	2.33±0.05	0.31	28.11±0.66	90.41±0.80	247.49±0.11
7	**D7**	2.34±0.05	0.33	24.56±0.31	93.41±0.80	248.87±0.32
8	**D8**	2.37±0.05	0.37	24.12±0.91	95.41±0.80	248.71±0.61
9	**D9**	2.63±0.05	0.32	22.08±0.52	98.41±0.80	248.87±0.53

(± SD SD = standard deviation)

ii) Wetting time and water absorption time:

Table No 7.6: Data for wetting time and water absorption time of Cinnarizine tablets

S No	Formulation code	Wetting time Sec (± SD)	Water absorption ratio % (± SD)
1	D1	52.48±0.86	59.33±2.89
2	D2	54.15±0.38	57.22±2.46
3	D3	51.86±0.30	57.33±1.12
4	D4	54.69±0.49	54.71±1.51
5	D5	56.54±0.21	63.26±1.86
6	D6	57.47±0.26	60.41±1.93
7	D7	52.33±0.26	61.47±0.26
8	D8	51.67±0.71	63.56±0.31
9	D9	47.47±0.56	67.47±0.26

iii) In-Vitro Disintegration Time of Cinnarizine

Table no 7.7: In-vitro disintegration data

formulation	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**
Disintegration time (sec)	**33.70**	**33.65**	**32.81**	**30.33**	**29.65**	**27.04**	**25.21**	**23.59**	**22.08**

iv) In - vitro dissolution study of Cinnarizine mouth dissolving tablets

Table No 7.8: Dissolution profile of formulation (D1-D3)

S No	Time (min)	D1	D2	D3
1	0	0	0	0
2	2	**24.31±0.72**	**28.33±1.16**	**21.70±0.96**
3	4	**29.14±0.68**	**34.27±0.90**	**27.55±0.68**
4	6	**33.72±0.85**	**40.52±0.87**	**32.86±0.85**
5	8	**39.47±0.97**	**47.87±0.73**	**38.06±0.93**
6	10	**45.93±0.63**	**53.05±0.98**	**44.83±0.97**
7	12	**55.28±1.08**	**66.49±1.07**	**53.63±1.37**
8	14	**64.85±0.89**	**77.68±0.67**	**62.12±0.74**
9	16	**72.60±0.75**	**85.10±0.79**	**69.19±0.92**
10	18	**79.31±0.90**	**94.75±0.81**	**78.27±0.98**
11	20	**82.73±0.41**	**97.54±0.11**	**82.48±0.16**

Fig No7.10: In-vitro dissolution profile of D1 to D3

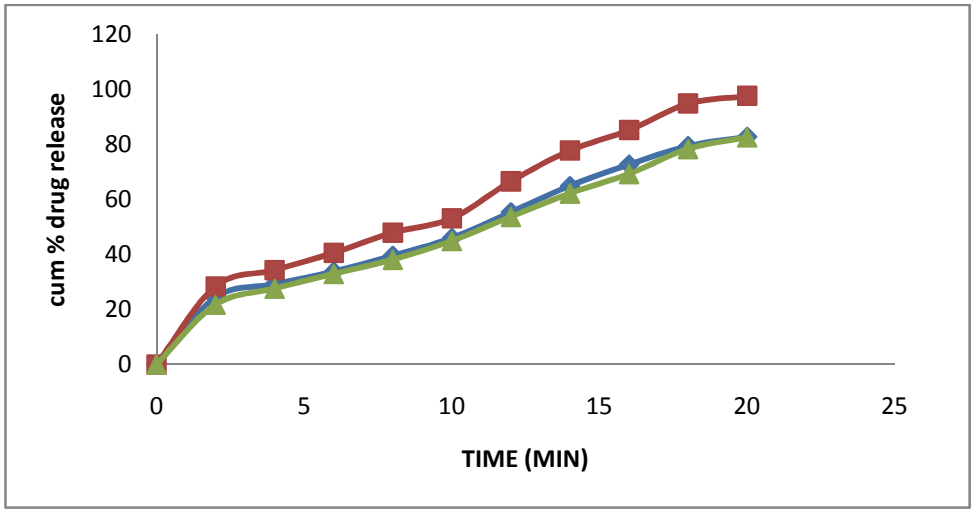


Table No 7.9: Dissolution profile of formulation (D4-D6)

S No	Time (min)	D4	D5	D6
1	2	26.94±0.91	28.33±1.16	21.94±0.91
2	4	32.47±1.12	34.27±0.90	30.47±1.12
3	6	38.31±0.67	41.52±0.38	36.31±0.17
4	8	45.05±0.80	47.87±0.73	45.05±0.08
5	10	52.18±0.76	51.05±0.81	53.18±0.76
6	12	63.80±0.85	61.49±1.07	64.80±0.85
7	14	74.52±0.59	74.68±0.67	72.52±0.59
8	16	85.63±1.20	79.10±0.79	81.63±1.20
9	18	91.70±0.94	93.75±0.81	93.70±0.94
10	20	93.65±0.48	95.47±0.42	95.35±0.75

Fig No 7.11: In-vitro dissolution profile of D4 to D6

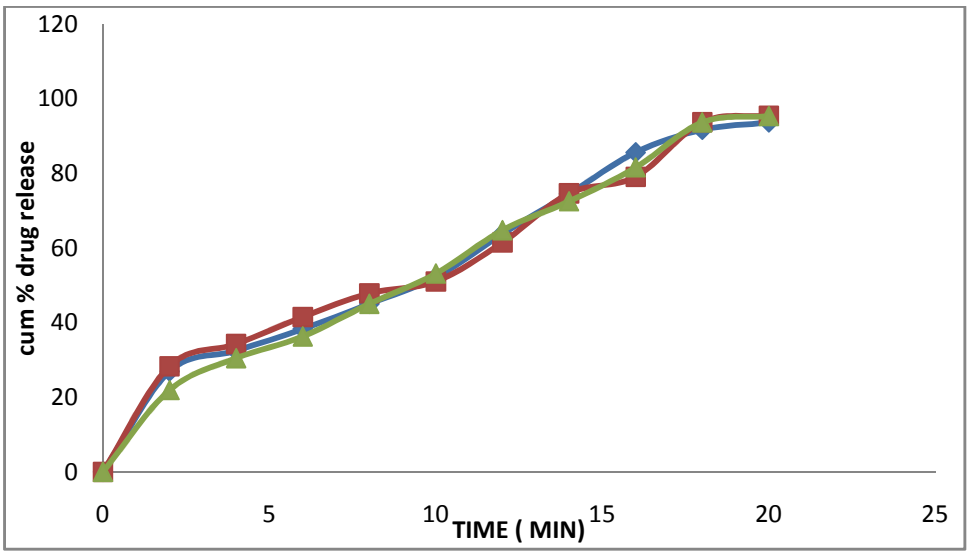


Table No 7.10: Dissolution profile of formulation (D7-D9)

S No	Time (min)	D7	D8	D9
1	2	23.70±0.96	23.70±0.96	26.94±0.91
2	4	26.55±0.68	27.55±0.97	35.47±1.12
3	6	32.86±0.85	32.86±0.85	42.31±0.67
4	8	38.06±0.93	31.06±0.73	48.05±0.80
5	10	44.83±0.97	49.83±0.37	54.18±0.76
6	12	53.63±1.37	63.63±1.37	67.80±0.85
7	14	62.12±0.74	67.12±0.74	79.52±0.59
8	16	69.19±0.92	73.19±0.92	90.63±1.20
9	18	78.27±0.98	78.67±0.98	98.70±0.94
10	20	81.75±0.15	81.34±0.38	99.43±0.56

Fig No 7.12: In-vitro dissolution profile of D7 to D9

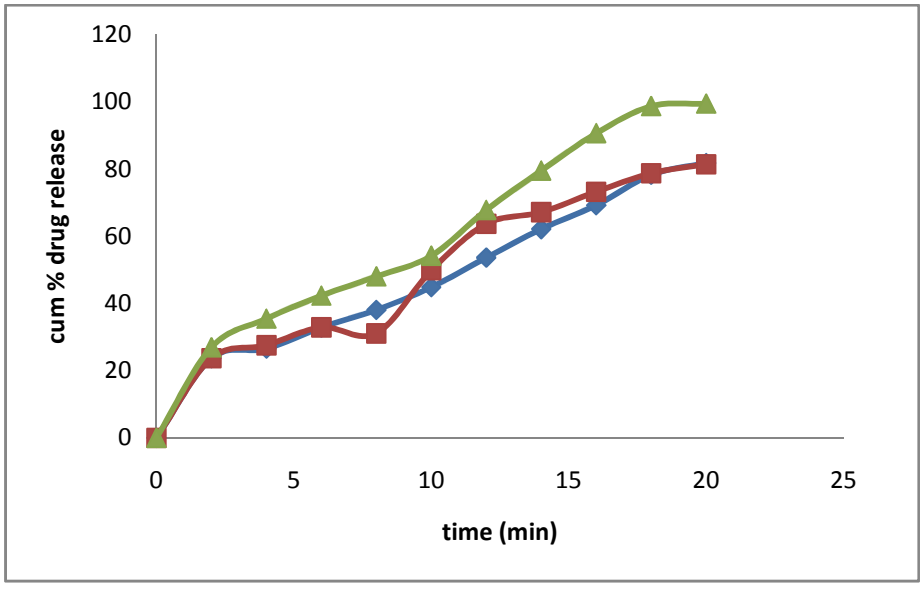
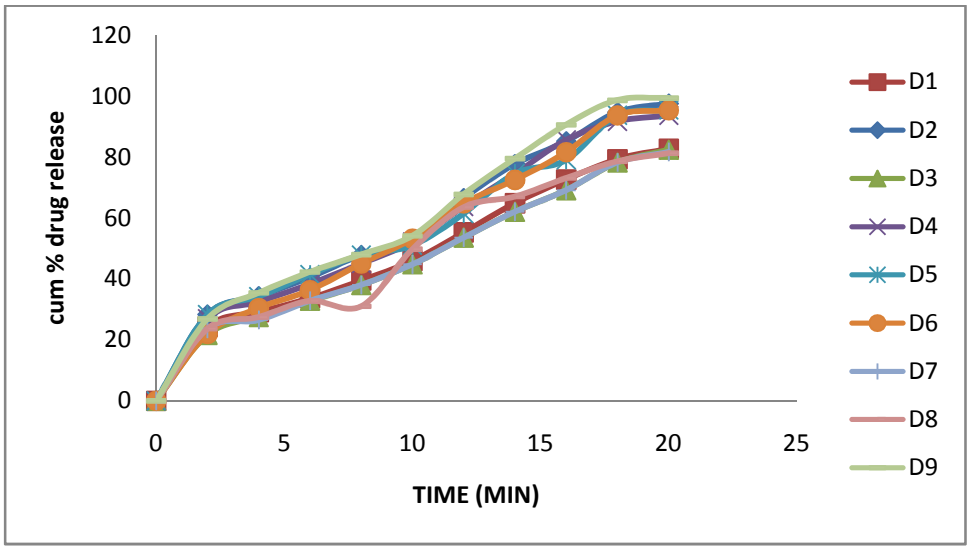


Table No 7. 11 : *In Vitro* dissolution data of formulations (D1-D9)

Time (min)	D1	D2	D3	D4	D5	D6	D7	D8	D9
2	24.31±0.72	28.33±1.16	21.70±0.96	26.94±0.91	28.33±1.16	21.94±0.91	23.70±0.96	23.70±0.96	26.94±0.91
4	29.14±0.68	34.27±0.90	27.55±0.68	32.47±1.12	34.27±0.90	30.47±1.12	26.55±0.68	27.55±0.97	35.47±1.12
6	33.72±0.85	40.52±0.87	32.86±0.85	38.31±0.67	41.52±0.38	36.31±0.17	32.86±0.85	32.86±0.85	42.31±0.67
8	39.47±0.97	47.87±0.73	38.06±0.93	45.05±0.80	47.87±0.73	45.05±0.08	38.06±0.93	31.06±0.73	48.05±0.80
10	45.93±0.63	53.05±0.98	44.83±0.97	52.18±0.76	51.05±0.81	53.18±0.76	44.83±0.97	49.83±0.37	54.18±0.76
12	55.28±1.08	66.49±1.07	53.63±1.37	63.80±0.85	61.49±1.07	64.80±0.85	53.63±1.37	63.63±1.37	67.80±0.85
14	64.85±0.89	77.68±0.67	62.12±0.74	74.52±0.59	74.68±0.67	72.52±0.59	62.12±0.74	67.12±0.74	79.52±0.59
16	72.60±0.75	85.10±0.79	69.19±0.92	85.63±1.20	79.10±0.79	81.63±1.20	69.19±0.92	73.19±0.92	90.63±1.20
18	79.31±0.90	94.75±0.81	78.27±0.98	91.70±0.94	93.75±0.81	93.70±0.94	78.27±0.98	78.67±0.98	98.70±0.94
20	82.73±0.41	97.54±0.11	82.48±0.16	93.65±0.48	95.47±0.42	95.35±0.75	81.75±0.15	81.34±0.38	99.43±0.56

Fig No 7.13: graph showing dissolution data for D1- D9



The in vitro dissolution study of all formulations (D1-D9) gives maximum drug release of 99.43% W/V for formulation D9 at the end of 20 min. all the formulations were within the limits for various post compression parameters like hardness, friability, weight variation and drug content.

Here, D9 given less disintegration time and better drug release after 20 min. Hence, D9 having Plantago Ovata as disintegrant was selected as the best formulation.

7.8 STABILITY STUDY

Optimized formulation D9 was subjected to stability studies 40 ± 2^0C / 75 ± 5% RH for 90 days. The product was evaluated for description, drug content and in vitro disintegration time. Drug release studies were conducted as per the procedure.

Descriptions:

Table no 7.12: Description

Storage condition	**Taste**	**Observation**	**inference**
RT	Descriptions	No changes of colour in all formulations	Complies with stability condition
40 ± 2^0C / 75 ± 5% RH	Descriptions	No changes of colour in all formulations	Complies with stability condition

Table No 7.13: Stability data of D9 formulation at 40 ï 2^{0}C / 75 ï 5% RH

Sl. No.	Time in days	Physical changes	Percent drug content* ±SD	*In vitro* Dispersion time* ±SD
1.	1st day (initial)	--	94.36±0.20	22.16±0.92
2.	30th day (1 month)	No changes	93.35±0.11	22.36±0.12
3.	60th day (2 month)	No changes	93.12±0.13	22.60±0.15
4.	90th day (3 month)	No changes	93.10±0.28	22.89±0.16

Average of three determinations; SD- Standard deviation

7.9. DISCUSSION

- **Preformulation Study**

In the preformulation study Cinnarizine was characterized for bulk, tapped density and angle of repose. Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties.

- **Compatibility Study**

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and superdisintegrant were studied. The characteristic absorption peaks of Cinnarizine were obtained at 2308cm^{-1}, 2503cm^{-1}, 3053cm^{-1}, 3358$cm^{-1}$and 3772cm^{-1}.The peaks obtained in the spectrum of each formulation correlates with the peaks of pure drug of Cinnarizine. This indicates that the drug was compatible with the formulation components.

- **Analytical Method**

Analytical method suitable to determine the contents of Cinnarizine was done by UV Spectroscopically. Cinnarizine shows the absorption maxima at 253.5 nm in 0.1N HCl (Ph 6.4) and absorption was linear through 1µg/ml to 10µg/ml. This method was found to be accurate, precise and specific for Cinnarizine.

- **Selection of Tabletting Methodology**

Effervescent method, Superdisintegrants addition method were tried for formulation of mouth dissolving tablets by direct compression technique. Super disintegration addition method exhibits the lowest disintegration time, hence it was concluded as the best method than compare to remaining methods.

- **Discussion of the effect of concentration Crosspovidone in the trial series.**

Batch D9 (10% plantago ovata) has lowest disintegration time (22.08 sec) than other batches but % friability is very high (0.39 %) and not in IP limit. Batch D7, D8 and D9 has0.36%,0.37% and0.39% friability in IP limit, from that D9 exhibits the lowest disintegration time, hence it was the best batch as compare to remaining batches.

- **Discussion of the characterization of the mouth dissolving tablets of Cinnarizine with various super disintegrants**

Agar , Gum karaya and Plantago ovata were tried for formulation of mouth dissolve tablets. The concentration of superdisintegrant was taken 4%, 6% and 10 %. The powder blend was evaluated for angle of repose, hausner's ratio and % compressibility. The prepared tablet was evaluated for physical parameter, Wetting time, In vitro disintegration time, Assay and In vitro drug release.

- **Evaluation of powder blend:**

1. Angle of Repose (¯)

The angle of repose for the entire formulations blend was found to be in the range 23.02^{o} to 26.40^{o}. Formulations with Plantago ovata and Gum karaya as a disintegrants showed angle of repose values $\leq 30^{o}$ where as formulation containing Agar showed angle of repose values $> 30^{o}$ indicating only fair flow property of the powder blend.

2. **Hausner ratio**

Hausner ratio was found to be in the range 1.12 to 1.16 and that indicated that all formulation has good flow properties.

3. **Carr's index**

Carr's index was found to be in the range 11.36% to 14.06% that indicated all formulation has good flow properties.

- **Physical Parameters**

1. Weight variation

All the formulated (D1 to D9) tablets were passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

2.Hardness

The hardness of the tablet was found to be 2.3 to 3.0 Kg/cm^2

3. Friability test

The maximum friability of the formulation was found to be 0.38%. The minimum friability of the formulation was found to be 0.31%. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

4. Drug content

The maximum drug content for the all formulation was found to be 98.41% and minimum % drug content from the all formulation was found to be 81.35%. The results were within the limit specified by the IP.

5. In vitro Disintegration test

In vitro Disintegration time was found to be in the range 22.08 to 33.70 sec. From all formulations, D9 (10% plantago ovata) has minimum disintegration time 22.08 sec. Formulations containing agar has taken more time for disintegration because of its gelling properties.

6. Wetting Time

Wetting Time was found to be in the range 47.47 to 57.47 sec. From all formulations, D9 (10% plantago ovata) has minimum wetting time.

7. In vitro drug release

All the 9 formulations were subjected to in vitro dissolution studies by using 0.1N HCl. Dissolution data shows that formulation D9 having having 10 %(Plantago ovata) gave improved dissolution as compared to other formulations and total drug release of 99.43% was found at 20 min

- **Stability Study**

Stability study was carried out for the optimized formulation according to ICH guide lines at 40±2° C (controlled sample), Room temperature and 40° C for 3 months.

The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

8. SUMMARY AND CONCLUSION

Cinnarizine is a histamine H_1-receptor antagonist is the most frequently prescribed drug in treatment of motion sickness, vomiting, allergic reaction, vertigo and insomnia. Conventional Cinnarizine tablets available in market are not suitable where quick onset of action is required. To overcome these problems, there is a need to develop a rapidly disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administered without water anywhere anytime. No such mouth dissolving tablet of Cinnarizine is available in the market.

In the present work, Mouth dissolving tablets were prepared by Effervescent, Superdisintegrant addition and evaluated for disintegration time, hardness and friability.

The Mouth dissolving tablets of Cinnarizine were prepared by superdisintegrants addition method using agar ,gum karaya and plantago ovate in different concentration like 4%, 6% and 10%. There are total nine formulations were prepared and evaluated for Weight variation, Thickness, Friability, Hardness, Disintegration time, Wetting time, Assay and In-vitro dissolution study.

The results of all formulations for Weight variation, Friability, Hardness and Assay were found to be within the IP limit and no significant variation. The Dispersion time for all formulations was found to be 22 to 33.70 seconds and wetting time was between 47.47 to 56.54 seconds. Based on the In-vitro dissolution studies, it was found that the drug release for all the formulations were within 30 minutes.

Formulation D9 containing plantago ovata in concentration of 10% showed minimum disintegration time, wetting time as compare to other formulations. Dissolution studies conclude that the total drug was released within 6 minutes. The results shown that disintegration time was increased in the following manners

Plantago Ovata < Gum Karaya < Agar.

The stability studies were performed for formulation D9 as per I.C.H guidelines, for its in-vitro disintegration time, wetting time and in-vitro drug release pattern. The formulation showed no significant variations for the above mentioned parameters and it was stable for the specified time period.

It was concluded that the mouth dissolving tablet of Cinnarizine can be formulated by superdisintegrant addition technique using Plantago ovate, Gum Karaya and agar in different concentrations.

BIBLIOGRAPHY

1) Brahmankar D. M., Jaiswal S.B., Biopharmaceutics & Pharmaceutics, First Edition, 1995, 335.

2) Howard C. Ansel, Nicholas G. Popvich, Loyd V. Allen, Pharmaceutical Dosage Forms and Drug Delivery System, First Edition, 1995, 78.

3) S. S. Biradar, S. T. Bhagavati and I. J. Kuppasad, Fast Dissolving Drug Delivery Systems: A Brief Overview, Internet J. Pharmacology, 2006, 4(2).

4) Kuccherkar B.S., Badhan A.C., Mahajan H.S., Mouth dissolving tablets: A novel drug delivery system, Phrma Times, 2003, 35, 3-10.

5) Kaushik D, Dureja H., Saini T. R., Mouth Dissolving Tablets: A review, Indian Drugs, 2004, 41(4), 187-193.

6) Amin A. F., Shah T. J., Bhadani M. N., Patel M. M., Emerging trends in orally disintegrating tablets, www.pharminfo.net, 2005.

7) Renon J. P. and Corveleyn S., Freeze-dried rapidly disintegrating tablets, US Patent No. 6,010,719, 2000.

8) Lailla J. K., Sharma A. H., Freeze-drying and its applications, Indian Drugs, 1993, 31, 503-513.

9) Seager H., Drug delivery products and zydis fast dissolving dosage form, J. Pharm. Phamacol., 1998, 50, 375-382.

10) Masaki K., Intrabuccaly disintegrating preparation and production, US Patent No. 5,466,464, 1995.

11) Pebley W. S., Jager N. E. and Thompson S. J., Rapidly disintegrating tablets, US Patent No. 5,298,261, 1994.

12) Allen L. V. and Wang B., Method of making a rapidly dissolving tablet, US Patent No. 5,635,210, 1997.

13) Allen L. V. and Wang B., Process for making a particulate support matrix for making rapidly dissolving tablets, US Patent No. 5,587,180, 1996.

14) Heinmann H. and Rothe W., Preparation of porous tablets, US Patent No. 3,885,026, 1975.

15) Knistch K.W., Production of porous tablets, US Patent No. 4,134,843, 1979.

16) Roser B. J. and Blair J., Rapidly soluble oral dosage form, method of making same and composition, US Patent No. 5,762,961,1998.

17) Lachmann L., Liebermann H. A. and Kiang J.L., The theory and practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, Bombay, 1998, 430-440.

18) Yarwood R. J., Kearny K. and Thomson A.R., Process for preparing solid dosage form for unpalatable pharmaceuticals, US Patent No. 5,738,875, 1998.

19) Parul B. Patel, Amit Chaudhary and G. D. Gupta, Fast Dissolving Drug Delivery Systems: An Update, www.pharmainfo.net, 2006.

20) Suresh B. Borsadia, David Halloran and James L. Osborne, Quick-dissolving films – A novel approach to drug delivery, www.drugdeliverytech.com, 2006.

21) Mishra B., Panigrahi D. and Baghel S., Mouth dissolving tablets: an overview of preparation techniques, evaluation and patented technologies, J. Pharm. Res., 2005, 4(3), 33-38.

22) Gregory G. K. E., Peach G. M. and Dumanya J. D., Method for producing fast dissolving dosage form, US Patent No. 4,371,561, 1983.

23) Mizumoto T., Masuda Y. and Fukui M., Intrabuccaly dissolving compressed moldings and production process, US Patent No. 5,576,014, 1996.

24) Robin H. Bogner and Meghan F. Wilkosz, Fast-Dissolving Tablets, www.uspharmacist.com, 2006.

25) Bhaskaran S. and Narmada, G. V., Orally disintegrating tablets, Indian Pharmacist, 2002, 1(2), 9-12.

26) Tablets: Formulation of tablets/Disintegration, www.pharmpedia.com, 2006.

27) Shah U. and Augsburger L., Evaluation of the functional equivance of crospovidone NF from different sources: standard performance test, Pharm. Develop. Tech., 2001, 6, 419-430.

28) Swarbrick J., Boylan J., Encyclopedia of Pharmaceutical technology; 2nd Ed., Marcel Dekker, NY, 2002, 2623-2638.

29) Gohel M., Patel M., Amin A., Agrwal R., Dave R. and Bariya, N., Formulation design and optimization of mouth dissolve tablets of nimesulide using vaccum drying technique, AAPS Pharm SciTech, 2004, 5(3), 1-6

30) Omaima A. Sammour, Mohammed A. Hammad, Nagia A. Megrab and Ahmed S. Zidan., Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion, AAPS Pharm SciTech, 2006, 7 (2) Article 55.

31) Mutasem M. Rawas-Qalaji, F. Estelle R. Simons and Keith J. Simons., Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics, AAPS Pharm SciTech, 2006, 7 (2) Article 41.

32) G. Abdelbary, P. Prinderre, C. Eouani, J. Joachim, J.P. Reynier and Ph. Piccerelle., The preparation of orally disintegrating tablets using a hydrophilic waxy binder, Int. J. Pharm., 2004, 278, 423–433.

33) Kei-ichi Koizumi, Yoshiteru Watanabe, Kumiko Morita, Naoki Utoguchi and Mitsuo Matsurnoto, New method of preparing high-porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material, Int. J. Pharm., 1997, 152, 127-131.

34) Shawn A. Mitchell, Thomas D. Reynolds and Tina P. Dasbach, A compaction process to enhance dissolution of poorly water soluble drugs using hydroxypropyl methylcellulose, Int. J. Pharm., 2003, 250, 3- 11.

35) G. Abdelbary., C. Eouani, P. Prinderre, J. Joachim, Jp. Reynier and Ph. Piccerelle, Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration, Int. J. Pharm., 2005, 292, 29–41.

36) Fukami J., Yonemochi E., Yoshihashi Y. and Terada K., Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose, Int. J. Pharm., 2006, 9, 101-109.

37) Shirwaiker A. A. and Ramesh M., Fast disintegrating tablets of Atenolol by dry granulation method, Indian J. Pharm. Sci., 2004, 66, 422-426.

38) Mishra D. N., Bindal M., Singh S. K. and Kumar S. G. V., Rapidly disintegrating tablets of valdecoxib, Indian Drugs, 2005, 42, 685-687.

39) Amin P. D., Gupta S. S., Prabhu N. B. and Wadhwani A. R., Fast disintegrating dosage form of ofloxacin and metrobenzole benzoate, Indian Drugs, 2005, 42, 614-617.

40) Remon J. P. and Corveleyn S., Formulation and production of rapidly disintegrating tablets by lyophiliization using hydrochlorothiazide as a model drug, Int. J. Pharm., 1997, 152, 215-225.

41) Chaudhari P. D., Khole S. R., Dave K. V. and More D. M., Formulation and evaluation of fast dissolving tablets of famotidine, Indian Drugs, 2005, 42, 641-649.

42) Vijaya K. S. G. and Mishra D. N., Rapidly disintegrating oral tablets of meloxicam, Indian Drugs, 2006, 43, 117-121.

43) Sreenivas S. A., Gadad A. P. and Patil M. B., Formulation and evaluation of ondansetron HCl directly compressed mouth disintegrating tablets, Indian Drugs, 2006, 43, 35-38.

44) Aithal K., Harish N. M., Rathanand M., Shirwaikar A. and Dutta M., Once daily fast dissolving tablets of Granisetron hydrochloride- formulation and invitro evaluation, Indian Drugs, 2006, 43(7), 576- 581.

45) Dandagi P. M., Halakatti P. K., Masthiolimath V. M., Patil M. B. and Manvi F. V., Rapidly disintegrating domperidone tablets, Indian Drugs, 2006, 43(7), 594-597.

46) Kuchekar B. S., Badhan A. C. and Mahajan H. S., Mouth dissolving tablets of salbutamol sulphate: A novel drug delivery system, Indian Drugs, 2004, 41(10), 592-598.

47) Nayak S. M. and Gopalkumar P., Design and optimization of fast dissolving tablets for promethazine theoclate, Indian Drugs, 2004, 41(9), 554-556.

48) Kaushik D., Dureja H. and Saini T. R., Formulation and evalution of olanzapine mouth dissolving tablets by effervescent formulation approach, Indian Drugs, 2004, 41(7), 410-412.

49) Devi V. K., Asha A. N., Pai R. S. Reddy M. C. H. and Raghvendra M. M. A. V., Oral dispersible fluconazole tablets - Preparation and evaluation, Indian Drugs, 2006, 43(7), 548-552.

50) H. S. ahajan, B. S. Kuchekar and A. C. Badhan, Mouth dissolve tablets of sumatriptan succinate, Indian J. Pharm. Sci., 2004, 66(3), 238- 240.

51) D. M. Patel, N. M. Patel, R. R. Shah, P. D. Jogani and A. I. Balapatel, Studies in formulation of orodispersible tablets of rofecoxib, Indian J. Pharm. Sci., 2004, 66(5), 621-625.

52) S. A Desai, S. V. Ferade, K. C. Petkar, D. S. Kuchkar, Orodissolving tablets of promethazine hydrochloride, Ind. J. Pharm. Edu. Res., 2006, 40(3), 172-174.

53) M. M. Patel and D. M. Patel, Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib, Indian J. Pharm. Sci., 2006, 68(2), 222-226.

54) Poornima D. Amin, Anita R. Wadhwani and Namita B. Prabhu, Patient compliant dosage form for Roxithromycin, Indian J. Pharm. Sci., 2004, 66(5), 670- 673.

55) Purnima Amin, Namita Prabhu and Anita Wadhwani, Indion 414 as super disintegrating in formulation of mouth dissolve tablets, Indian J. Pharm. Sci., 2006, 68(1), 117-119.

56) Mane Avinash R. and Kusum Devi V., A novel technique for the preparation of mouth dissolving tablets of domperidone, Indian Drugs, 2003, 40(9), 544-546.

57) Shishu and Bhatti A., fast disintegrating tablets of diazepam, Indian Drugs, 2006, 43(8), 643- 648. s

58) Gordan M. S., Rudraraju V. S., Rhie J. K. and Chowan Z. T., The effect of aging on the dissolution of wet granulated tablets containing super disintegrants, Int. J. Pharm., 1993, 97, 119-131.

59) Machida Y., Inouye K., Tokumura T., Iwata M. and Nagai T., Preparation and evaluation of intragastric buoyant preparations, Drug Des. Deliv., 1989, 4, 155-161.

60) J. M. Gines, M. D. Veiga, M. J. Arias and A.M. Rabasco, Elaboration and thermal study of interactions between cinnarizine and gelucire® 53/10 physical mixtures and solid dispersions, Int. J. Pharm., 1995, 126, 287-291.

61) Greg A. Kossena, William N. Charman, Ben J. Boyd and Christopher J. H. Porter, A novel cubic phase of medium chain lipid origin for the delivery of poorly water soluble drugs, J. Control. Release, 2004, 99, 217–229.

62) Cinnarizine, www.redpoll.pharmacy.ualberta.ca/drugbank/index.html, 2006.

63) British Pharmacopoeia, Cinnarizine, The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA),2001, 398- 400.

64) James E F Reynolds: Martindale, The extra Pharmacopoeia, Thirty-First edition, Royal Pharmaceutical Society, London, 1996, 406.

65) Cinnarizine: drug information, www.emc.medicines.org.uk, 2006.

66) CIMS-93 April-2006 (update-2), 211-212.

67) Handbook of Pharmaceutical Excipient Third Edition, Edited by Arthur H. Kibbe, 102-103.

68) Information of suerdisintegrants, www.pformulate.com, 2006.

69) Crospovidone, www.nppharm.fr.com, 2006.

70) Herbert A. Liberman and Leon Lachman, The Theory and Practice of Industrial Pharmacy, Third Edition, Verghese Publication House, 171, 293.

71) Cooper J, Gun C, Powder Flow and Compaction, Tutorial Pharmacy, New Delhi, hidix CBS Publishers and Distributors, 1986, 211-233.

72) Indian Pharmacopoeia, Fourth Edition, controller of Publication., Govt. of India., New Delhi, 1996, A-86.

73) Kulkarni G T, Gowathamarajan K, Suresh B, Stability testing of Pharmaceutical product: an overview, Ind. J. Pharm. Sci., 2004, 38(4), 194-202.

74) ICH Q1A (R2), Stability Testing Guidelines, Stability testing of a new drug product and new drug substance.